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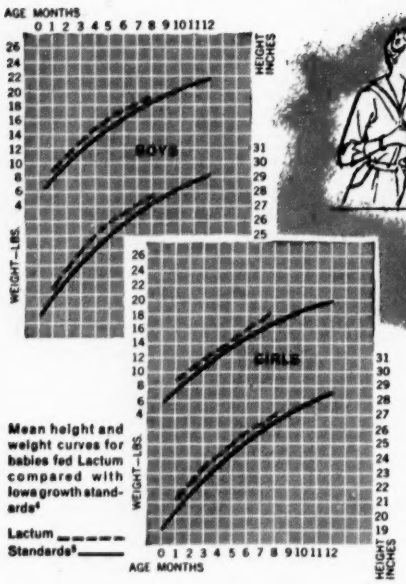

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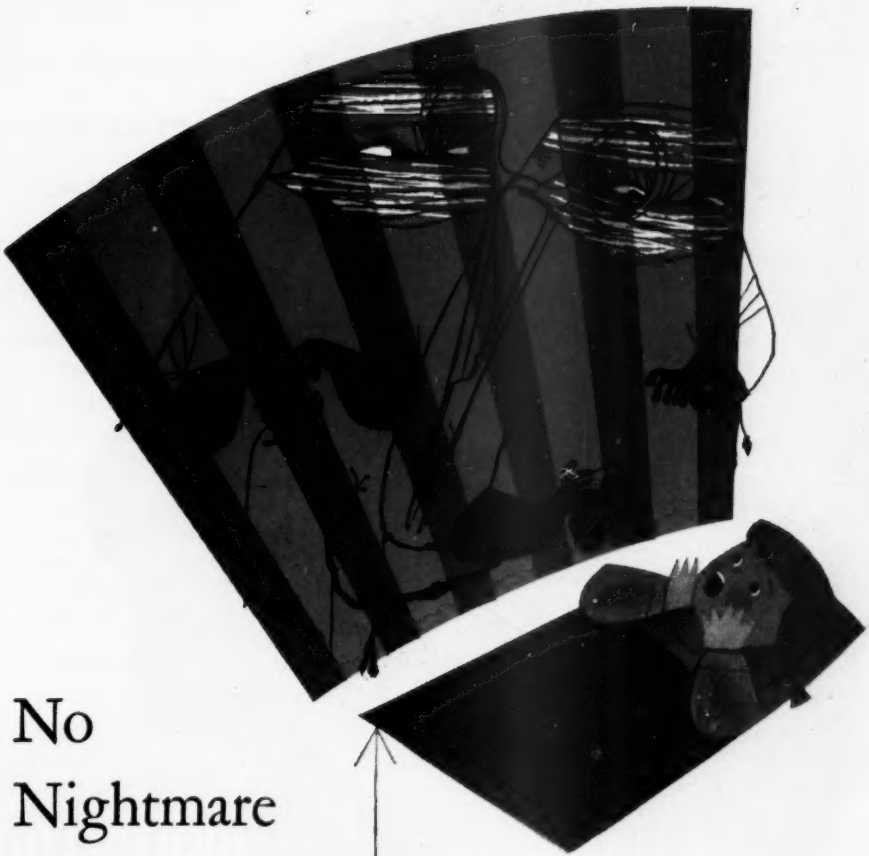

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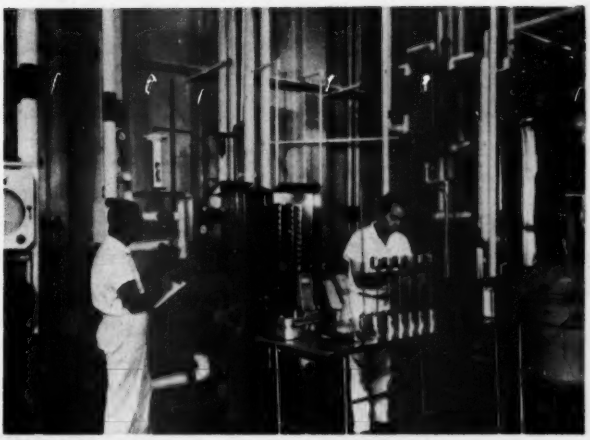

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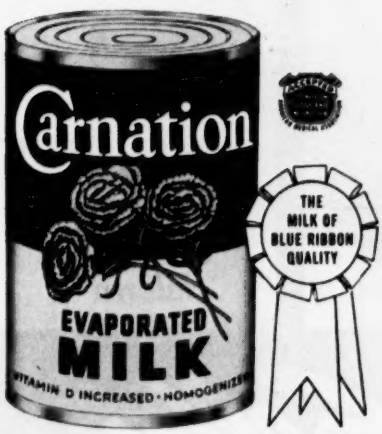

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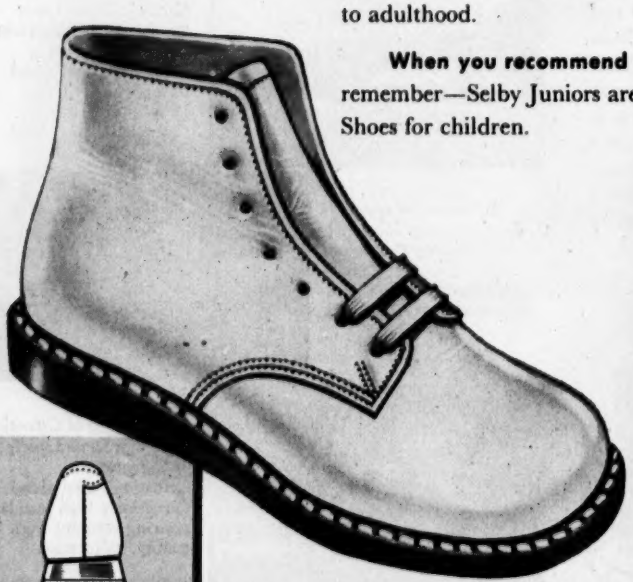

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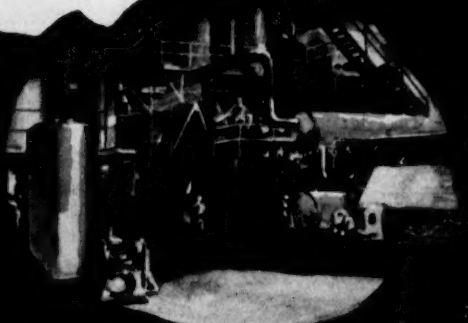
School children	47%	Low intake of C	J. Am. Dietet. A. 28:718, 1952.
College students eating at dining halls	53%	Low blood levels of C	J. Am. Dietet. A. 24:957, 1948.
Patients with paradentosis	62% of daily meals analyzed were deficient in C	C intake below recommended levels	J. Periodont. 23:228, 1952.
Institutional inmates over 50	44%	C intake below recommended levels	Calif. Med. 74:105, 1951.
	87%	Low blood levels of C	



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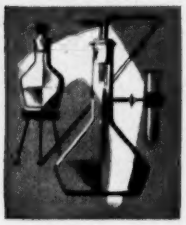

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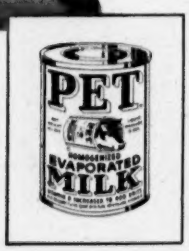

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A. M. A.
American Journal of Diseases of Children

VOLUME 87 JUNE 1954 NUMBER 6

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SERUM VITAMIN A AND CAROTENE LEVELS IN CHILDREN WITH RHEUMATIC FEVER

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IOWA CITY

RHEUMATIC fever has long been recognized as a disease occurring most frequently in children receiving poor environmental care. In the past two decades, the nutritional background of children with rheumatic fever has attracted growing interest.* At the present time, however, it is still not clear whether or how suboptimal nutrition, acting in conjunction with other adverse living conditions, such as poor housing, overcrowding, repeated exposures to infections, and less protection from physical and emotional stresses, increases the susceptibility and modifies the response of the hosts to the disease. Jackson and others [4] found that the recurrence rate of rheumatic fever was lowered in children who had special attention devoted to improvement in their environments, including nutrition. Of the various factors possibly involved, the most significant association was observed between the dietary ratings and the recurrence rate of the disease. They found a significant correlation (inverse) between the adequacy of the diet and the recurrence rate of rheumatic fever. Coburn and associates [2] noted combined deficits in protein, vitamin A, calcium, and iron in the diets of a group of rheumatic children and later [5] demonstrated a drop in plasma vitamin A levels coincident with the development of acute rheumatic fever. The degree of reduction of the vitamin level varied directly with the severity of the attack.

In the present study, values of serum vitamin A and carotene have been determined in a group of children with rheumatic fever throughout the entire course of the disease. The effects of diet, of intercurrent infections and of exacerbations of the rheumatic process, the severity of heart damage, the presence of decompensation, and the effect of the administration of corticotropin (ACTH) on plasma levels of vitamin A and carotene have been studied. The rates of absorption and excretion of vitamin A after ingestion of a large test dose have also been investigated.

From the Department of Pediatrics, State University of Iowa College of Medicine.
This study was supported, in part, by a research grant from Hoffmann-LaRoche, Inc.
* References 1-4.

CLINICAL MATERIAL

From September, 1948, to June, 1952, 302 pairs of fasting serum vitamin A and carotene levels were determined on 98 patients with rheumatic fever. The ages of the children ranged from 5 to 16 years. The Jones criteria were used in establishing the diagnosis of rheumatic fever.[6]

This study has included patients in the acute stage of the illness, in the period of gradual convalescence in the hospital, and, also, inactive patients observed in the outpatient clinic. A detailed nutritional history was obtained for each patient upon admission and in the subsequent visits. The dietary rating was made from the analysis of the dietary intake of the child for the period six months prior to the onset of rheumatic fever. The diet of the children in the hospital was so planned as to contain an adequate amount of all essential dietary constituents, particularly animal protein, and was supplemented with 1 teaspoonful (4 to 5 ml.) of cod liver oil daily (3,000 I. U. of vitamin A). At the time of dismissal of the patients, the parents were given detailed dietary instructions by the dietitian and were advised to give 1 teaspoonful of cod liver oil daily. Throughout the period of observation, clinical and laboratory studies, including erythrocyte sedimentation rate, plasma mucoprotein, and electrophoresis of the serum proteins, were obtained at various intervals.

The course of rheumatic fever was divided into acute, subacute, and inactive stages. The acute stage corresponds roughly to the early exudative processes of the disease, during which time the patients have various symptoms, such as fever, general malaise, pain and swelling of the joints, shortness of breath, and pain in the chest or abdomen. The subacute stage corresponds to the proliferative processes of the disease, during which time the patients are essentially free from symptoms but have abnormal laboratory values, such as elevation of the erythrocyte sedimentation rate and plasma mucoprotein. Each of the stages is subdivided again into early and late, in order to establish the status more precisely for evaluation of the clinical data.

A number of children in the acute and some in the subacute stages of rheumatic fever received corticotropin and cortisone. The corticotropin was given in the dosage of about 1 mg. per pound (0.5 kg.) of body weight daily in six to eight divided doses for two to four weeks. Then the dosage was reduced gradually to nothing over a period of four to six weeks.

The concentration of vitamin A and carotene in serum was determined with the use of activated glycerin dichlorohydrin after the method of Sobel and Snow.[7]

Absorption tests were performed on 46 children in varying stages of rheumatic fever. Six thousand international units of vitamin A per pound of body weight, either in the form of concentrated natural vitamin A in an oily base † or synthetic vitamin A palmitate in an aqueous medium,‡ was given. The serum vitamin A levels were obtained before and four and nine hours after the administration of the test dose.

Feces were collected from 12 of these children for a period of two to four days for the determination of the vitamin A excretion after such a single large dose was given.

† Percomorph liver oil (Oleum Percomorphum), Mead Johnson & Company.

‡ Hoffmann-LaRoche, Inc.

The normal ranges of carotene and vitamin A in serum have not been specifically set. It has been shown that the serum level of vitamin A, except perhaps in prolonged deficiency of this vitamin, is unrelated to the amount of liver storage.§ From survey studies,‖ mean values for various groups range from 30 to 40 γ per 100 ml., but it appears that well-fed healthy children usually show plasma vitamin A values above 40 γ per 100 ml. The values found in the newborn infant, 20 to 30 γ per 100 ml., may be considered as minimum normal values. Serum carotene values vary directly with the intake, and in well-fed healthy children range from 100 to 300 γ per 100 ml.

I. *The Levels of Serum Vitamin A and Carotene in Relationship to the Stages of Rheumatic Fever.*—One hundred ninety-two pairs of observations of serum vitamin A and carotene levels were made of 71 typical rheumatic children at various periods from the early onset of the attack of rheumatic fever and for years after the disease was inactive. The values obtained during the course of the disease when there was an intercurrent infection, severe cardiac damage, or an acute exacerbation of the rheumatic processes have been excluded from this typical group and analyzed

TABLE 1.—*The Levels of Serum Vitamin A and Carotene in the Varying Stages of Rheumatic Fever*

	No. Observations	No. Patients	Vitamin A, γ/100 Ml.				Carotene, γ/100 Ml.			
			Min.	Mean	Max.	S.D.	Min.	Mean	Max.	S.D.
Early acute	15	13	12.0	32.1	62.0	15.2	20.4	58.2	98.5	20.7
Late acute	25	22	13.3	35.0	50.2	9.2	32.0	82.2	148.0	30.5
Early subacute	18	18	21.9	44.8	74.0	13.4	47.0	104.9	193.5	45.8
Mid subacute	32	27	32.5	66.2	149.0	23.6	58.0	179.5	450.0	87.0
Late subacute	40	29	35.7	62.5	137.0	22.9	74.8	179.3	368.0	83.7
Recent inactive	32	31	33.2	72.5	133.0	24.0	24.0	128.0	342.3	71.3
More than 6 mo. inactive	30	24	31.0	58.8	108.0	19.0	33.0	101.3	212.0	41.7

separately. The mean, standard deviation, and range of the serum vitamin A and carotene values were computed for various stages of the disease and are shown in Table 1. Examination of Table 1 shows that, though the maximum values observed in each group were ample, the mean vitamin A value during the acute stage of rheumatic fever was somewhat lower than the 40 γ per 100 ml. considered desirable. The minimum values observed were definitely low, and 73% of the observations were less than 40 γ per 100 ml. In the subacute stages, maximum values were at a high level, and the mean values for the group were normal, but the minimum values, though well above those noted in the acute stage, were slow in rising. In the late subacute stage, only 5% of the values were below 40 γ per 100 ml. In each group studied, some children showed low values, while others at an equivalent stage of the disease showed very high values. It has been observed that when the vitamin A intake is high, serum vitamin A values are well above 40 γ per 100 ml. and that wider individual differences are found than when the intake is low. In general, the number of low values decreased as convalescence proceeded. However, serum vitamin A levels between 30 and 40 γ per 100 ml. were observed in all stages. Values under 30 γ were observed only in the acute and early subacute stages of the disease.

§ References 8-9.

‖ References 10-12.

Except perhaps in early acute rheumatic fever, mean carotene levels were adequate. Low values for minimum carotene levels were observed as often in inactive as in acute rheumatic fever and, therefore, probably represent merely a low carotene intake.

Almost all of the children in the acute stages of the disease were admitted to the hospital shortly after the onset of symptoms and signs of rheumatic fever. Thirteen observations (32% of vitamin A and carotene levels made in the acute stage of the disease were of children whose dietary intake was either suboptimal or definitely inadequate. The mean serum vitamin A and carotene concentrations of these 13 children, however, were 35.6 γ and 70 γ per 100 ml., respectively, which are not significantly different from the mean values of the total group of patients, 32.1 and 58.2 γ per 100 ml., observed during the acute stage. This small difference cannot be easily evaluated because of the many variables present in the acute stage. Because of the storage of vitamin A in the human body,¶ the brief initial anorexia and decreased intake of vitamin A in the acute stage of rheumatic fever would not of itself account for the decrease of serum vitamin A. On the other hand, carotene is never stored in any appreciable amount and is converted into vitamin A.[15] The level of carotene in the serum drops rapidly with the reduction of dietary intake in the acute stage.

Two of the 15 observations in the early acute and 9 of the 25 in the late acute stage of the disease were made when the children were afebrile or had a very slight temperature elevation. The remaining 29 observations were made when the children had elevation of temperature ranging from 100 to 103 F. on the day of observation and the preceding week or the subsequent week. Of the 11 observations when the children were afebrile, the average value of serum vitamin A was 38.8 γ per 100 ml., and of carotene, 78.6 γ per 100 ml., as compared to 32.1 and 71.2 γ per 100 ml. at the time of fever. These data suggest that children in the acute stage of rheumatic fever, with temperature elevation, tend to have a slightly lower serum vitamin A level than children without temperature elevation.

II. *The Levels of Serum Vitamin A and Carotene in Relation to the Severity of Cardiac Damage and Passive Congestion of the Liver.*—Thirty-one pairs of observations of serum vitamin A and carotene were made of children who had suffered from severe cardiac damage with or without evidence of cardiac decompensation. Almost all of these children had a history of repeated attacks of rheumatic fever in the past; the remaining few were having chronic remittent type of rheumatic fever with extensive carditis. The children in advanced cardiac failure showed marked enlargement of liver, pulmonary congestion, and peripheral edema. Ten observations were made of children with severe damage, pronounced cardiac enlargement (cardiothoracic index, 0.62 to 0.85) and hepatomegaly. Another six serum specimens were obtained from children with a cardiothoracic index ranging from 0.61 to 0.65, without hepatic enlargement. The diet offered to them was adequate and was supplemented with approximately 3,000 to 5,000 I. U. of vitamin A. Unfortunately, their intake of vitamin A and carotene from food varied greatly because of wide variations in appetite. The analysis of these data on children grouped according to severity of cardiac damage and enlargement of the liver is shown in Table 2. The degree of

¶ References 13-14.

lowering of the serum vitamin A and carotene varies directly with the passive congestion and enlargement of the liver. All of these patients were in the subacute or inactive stages of rheumatic fever. The vitamin A values observed in this group were similar to those noted in the acute stage of the disease. Serum carotene levels were not seriously affected unless there was passive congestion, which is invariably associated with anorexia and vomiting.

III. *Levels of Serum Vitamin A and Carotene in Chorea.*—There were 14 observations made of nine children with active chorea who were afebrile and had no other manifestations of rheumatic fever. Their erythrocyte sedimentation rates were within normal range at the time of study. The average values of both the serum

TABLE 2.—*The Relationship of Serum Vitamin A and Carotene Level and the Severity of Cardiac Damage* *

	No. Observations	No. Patients	Vitamin A, γ/100 Ml.				Carotene, γ/100 Ml.			
			Min.	Mean	Max.	S.D.	Min.	Mean	Max.	S.D.
Advanced cardiac decompensation with enlargement of liver	15	4	17.0	32.0	79.0	18.5	33.0	75.9	158.0	28.9
Severe cardiac damage with enlargement of liver	10	4	16.0	39.3	65.0	16.3	43.0	86.5	185.5	26.4
Severe cardiac damage without enlargement of liver	6	3	39.0	52.1	72.0	12.9	80.0	124.8	146.0	23.0

* All patients were in the subacute or inactive stages of rheumatic fever.

TABLE 3.—*The Levels of Serum Vitamin A and Carotene in Chorea, Recent Upper Respiratory Infection, Acute Exacerbation of Rheumatic Processes, and During the Administration of Corticotropin (ACTH)*

	No. Observations	No. Patients	Vitamin A, γ/100 Ml.				Carotene, γ/100 Ml.			
			Min.	Mean	Max.	S.D.	Min.	Mean	Max.	S.D.
Chorea	14	9	35.3	65.7	137.0	29.9	60.0	187.5	410.0	106.0
Recent intercurrent infection	25	18	22.0	39.6	68.0	12.9	28.0	144.7	294.0	70.7
Acute exacerbation of rheumatic processes	9	7	17.7	34.6	57.0	11.5	88.0	172.4	300.0	66.3
During administration of corticotropin	22	14	50.0	92.6	210.0	41.3	70.0	144.7	188.0	33.5

vitamin A and carotene are high normal or above and similar to the average levels in the mid- and late-subacute stages of rheumatic fever, but the ranges of the values are much wider (Table 3).

IV. *Effects of Intercurrent Infection and Acute Exacerbation of Rheumatic Processes on the Levels of Serum Vitamin A and Carotene.*—During the subacute and inactive stages of rheumatic fever, 18 children developed or were recovering from upper respiratory infections at the time of 25 of the observations. Except for two patients who had a moderate degree of temperature elevation, the remainder were afebrile. One patient had an erythrocyte sedimentation rate of 75 mm. at the end of 45 minutes (Westergren); the remainder had rates below 41 mm., of which eight were within normal limits. In Table 3, it is seen that the patients had lowered levels of serum vitamin A during the acute upper respiratory infection, even though most of them had normal body temperatures. Nine observations were made of children during the subacute stage of the disease with an acute exacerbation. With acute exacerbation of the rheumatic processes in this group of children, the mean

values of serum vitamin A dropped below those observed in the patients with intercurrent upper respiratory infections. Individual curves of serum vitamin A levels of patients with infections or exacerbation are shown in Chart 1. The levels of serum carotene were not significantly changed by these complications during the subacute stage of the disease.

It still remains to be seen if the depression of serum vitamin A during febrile infectious diseases is caused by elevation of body temperature or by infectious processes per se.# In the present study, it has been found that the serum vitamin A levels in children during the acute stage of the disease whose temperatures were normal or but slightly elevated were higher than in those children having definite fever. But some other explanations must be given for the lowering of the serum

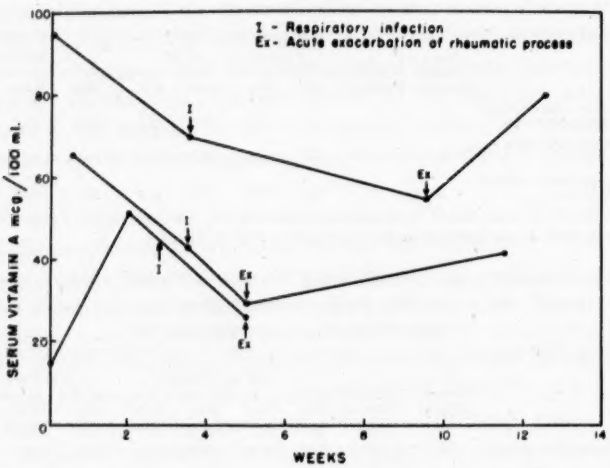

Chart 1.—The effect of intercurrent respiratory infection and acute exacerbation of the rheumatic processes on the level of serum vitamin A during the subacute stage of rheumatic fever. In Charts 1 through 4, the abbreviation mcg. (micrograms) refers to the same measurement as the γ used in the text.

vitamin A level in children in the acute stage who had been afebrile for some time prior to the observation and also in children having normal temperatures despite intercurrent infection.

V. *The Levels of Serum Vitamin A and Carotene During Corticotropin Administration.*—Twenty-two observations of serum vitamin A and carotene levels were made of 14 children during the period when corticotropin was given. Nine observations were made when the children were in the acute stage of the disease, five in the subacute stage, and one when the child was having active chorea. During the first five days of corticotropin administration, there was a slight increase of the serum concentration of vitamin A. After this initial period, an even larger increase took place. Three of the highest readings were 145, 188, and 210 γ per 100 ml. The average value of the serum vitamin A level was 92.6 γ per 100 ml., which was 20 γ higher than the average value obtained for the recently inactivated patients. The

References 13 and 16-19.

relation of this marked elevation of serum vitamin A and the corticotropin administration is presented in Chart 2. The serum vitamin A in patients in the subacute stage of the disease apparently responded to corticotropin administration in a way similar to that of patients in the acute stage of the disease. Patients in the acute stage showed rapid increase in serum carotene level after receiving corticotropin. The trend was reversed in the subacute stage, that is, the serum carotene level in patients receiving corticotropin was much lower than in those who did not receive it. Children who were receiving corticotropin developed a voracious appetite and

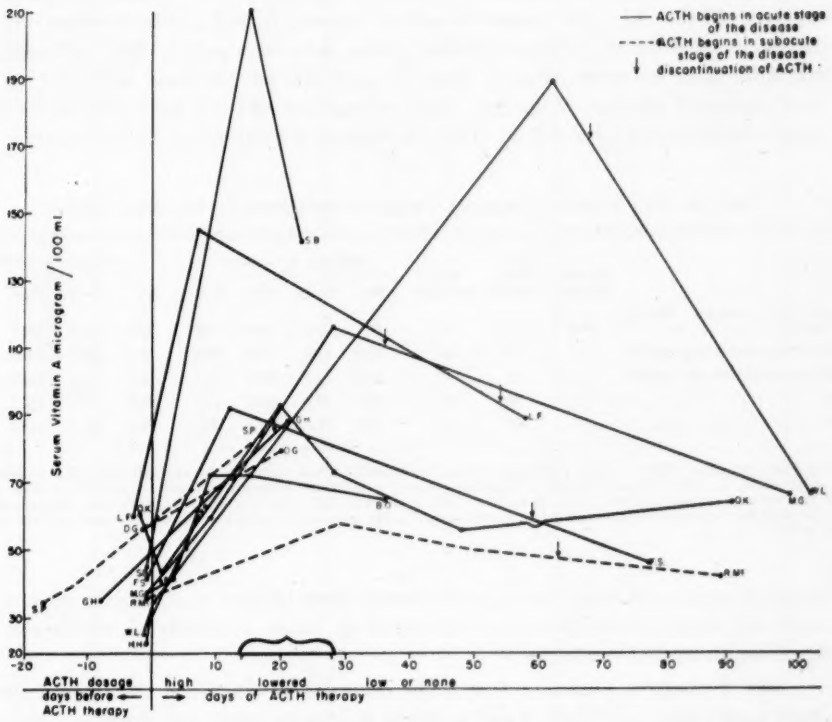

Chart 2.—The changes in serum vitamin A levels during the course of corticotropin (ACTH) administration.

were given a well-balanced diet. The lower level of serum carotene observed in this group of patients in the subacute stage of the disease, as compared to the abnormally high levels observed in patients in the same stage of the disease but not receiving corticotropin, may indicate that corticotropin accelerates the conversion of carotene to vitamin A in the body.

VI. *The Vitamin A and Carotene Intake in Relationship to the Levels in the Serum.*—The children whose diets were rated as poor to fair (Table 4) were primarily those coming into the hospital with subacute rheumatic fever or with chorea. Mean values for serum vitamin A were adequate, but minimum values were

low. With few exceptions, those children whose home diets were rated good or excellent showed high serum vitamin A. The occasional low carotene values observed were considered more indicative of low intake of vegetables than of poor ability to absorb carotene. The average daily intake of vitamin A and carotene in children whose diet was rated as good was from approximately one and one-half to two times the recommended daily allowance for age and sex. With a vitamin A supplement equivalent to 1 teaspoonful daily of standardized cod liver oil, the diet was rated as excellent. This supplement increased the intake of vitamin A at least another 100% of the recommended daily allowance. The addition of vitamin A as cod liver oil to an adequate diet made no significant difference in the levels of serum vitamin A and carotene (Table 4). The ranges of serum vitamin A and carotene values are definitely lower for the group of children whose diets were poor to fair. Although the mean value for serum vitamin A was 49 γ per 100 ml., the mean values for the four groups of children receiving a good to excellent diet fell within the narrow range of 65.8 to 68.1 γ per 100 ml. These differences are significant, but it is possible

TABLE 4.—*The Relation of Ingested Vitamin A and Carotene to the Serum Levels*

	Dietary Rating *	No. Observations	No. Patients	Vitamin A, γ/100 Ml.				Carotene, γ/100 Ml.			
				Min.	Mean	Max.	S. D.	Min.	Mean	Max.	S. D.
Mid and late subacute, inactive, and chorea	P-F	14	12	27.1	49.1	80.0	13.6	33.0	90.9	193.5	42.3
Mid and late subacute and chorea	E	57	38	32.5	65.8	149.0	26.6	70.0	182.1	368.0	73.3
Mid and late subacute and chorea	G	19	17	40.0	68.1	126.0	21.4	60.7	205.8	459.0	106.2
Inactive	E	39	30	40.0	67.2	133.0	21.6	24.0	118.5	342.0	66.1
Inactive	G	17	15	31.0	65.9	108.0	26.6	70.0	121.6	218.5	44.2

* E indicates excellent—Diet contains adequate amount of vitamin A and carotene for age and sex and is supplemented with 1 teaspoonful (4-5 ml.) of cod liver oil; G indicates good—Diet contains adequate amount of vitamin A and carotene for age and sex and is not supplemented with cod liver oil; F indicates fair—Diet contains vitamin A and carotene, but not more than that recommended for age and sex; P indicates poor—Diet contains inadequate amount of vitamin A and carotene for age and sex.

that the group of children receiving the poorest diets because of inadequate general care may have had more intercurrent infections which invariably would depress their serum level of vitamin A.[17]

VII. *Vitamin A Tolerance Test.*—The results of 51 vitamin A absorption tests have been plotted in Charts 3 and 4, where it is to be noted that there is a wide distribution of the serum vitamin A levels at four hours and nine hours after the administration of a single large dose (6,000 I. U. per pound of body weight) of vitamin A in both aqueous and oily preparations. At the end of four hours, 19 of 28 values (65.7%) of children receiving an aqueous preparation were above 400 γ per 100 ml., while only 6 of the 23 values (26.1%) of those receiving an oily preparation were above the stated level. Three children receiving an oily preparation absorbed the vitamin very slowly, as shown by the higher serum vitamin A level at the end of nine hours than at four hours, whereas all of the other children showed a higher serum vitamin A level at four hours. On account of the wide distribution of the values of serum vitamin A at given times after receiving the test dose of vitamin A, there are no consistent differences in the absorption of vitamin A between the varying stages of rheumatic fever in patients receiving corticotropin, or in those

with cardiac decompensation. The response of the patients receiving corticotropin was more uniform than of those not receiving corticotropin. The tolerance curve cannot be predicted from the fasting vitamin A level.

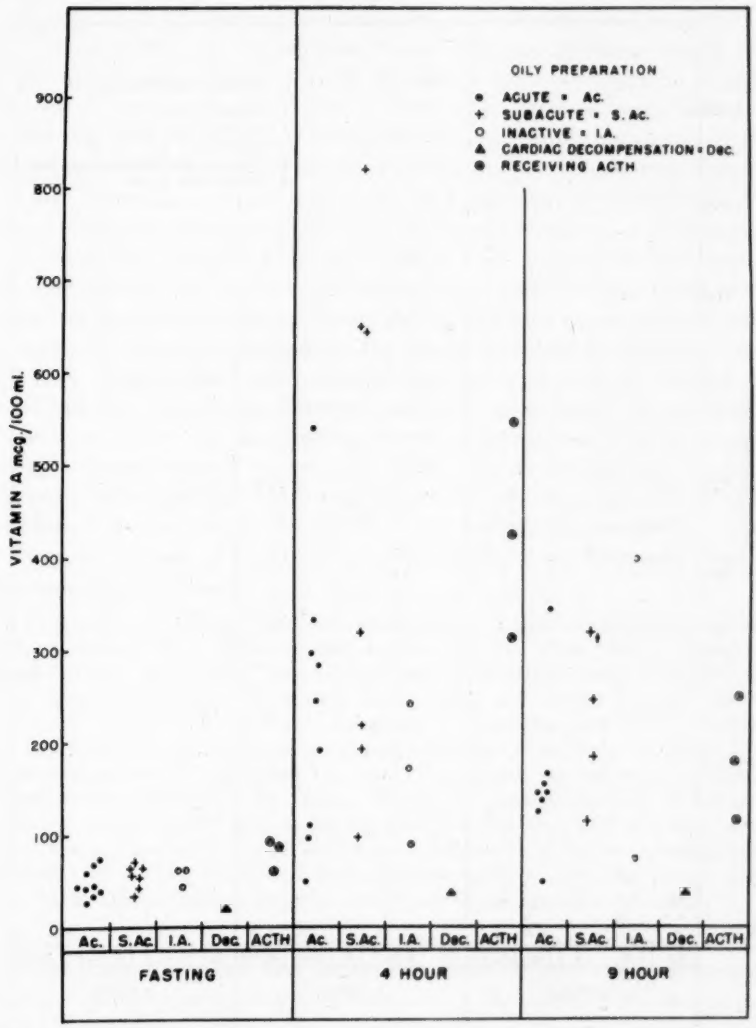

Chart 3.—The levels of serum vitamin A before and during 23 absorption tests using an oily preparation of vitamin A.

Delayed absorption of vitamin A in rheumatic children was reported by Shank, Coburn, Moore, and Hoagland, using a natural ester in oily bases.[5] It has been established that aqueous vitamin A is absorbed more efficiently than the oily preparations.*

* References 20-21.

In the present study, the aqueous preparation of vitamin A has been found to be very well absorbed, with a few exceptions, by children in the varying stages of rheumatic fever and also by children with congestive heart failure. The oily prepa-

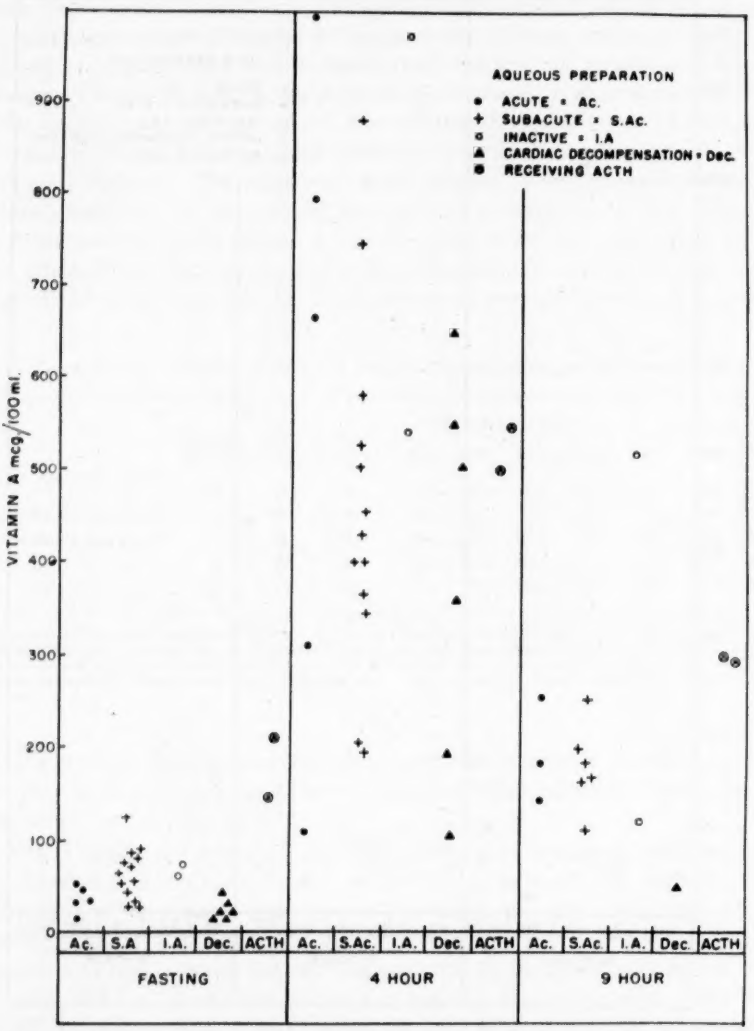

Chart 4.—The levels of serum vitamin A before and during 28 absorption tests using an aqueous preparation of vitamin A.

ration of vitamin A was not absorbed as fast. It is felt that the peaks of absorption in some of the children receiving an oily preparation might have been missed because the serum vitamin A levels were not read frequently enough after the testing dose was given.

It seems quite unlikely that the lowering of serum vitamin A level in the early acute stage is related to absorption. It has been shown that the plasma vitamin A may remain unchanged for several months when the oral intake of vitamin A and carotene in the diet is greatly reduced.† In view of this, the serum vitamin A levels in the early stages of rheumatic fever cannot be affected by any sudden alteration of absorption with the onset of the disease, if there is such an alteration. Moreover, the rapidly rising serum vitamin A levels throughout early convalescence in patients who were not receiving large amounts of vitamin A or carotene clearly indicate that the lowering of serum vitamin A at this time is not a sign of true vitamin A depletion, which would be present in patients suffering from chronically poor absorption.

VIII. *Excretion in Feces After a Single Large Dose of Vitamin A.*—After vitamin A tolerance tests, using either aqueous or oily preparations, fecal specimens were collected from seven children for two days, from one child for three days, and from four children for four days. Large amounts of vitamin A were found excreted through the gastrointestinal tract. During the first 24 hours, almost all of the patients excreted small amounts of vitamin A. The amount increased during the second and third days. Some children were still excreting vitamin A in large amounts at the end of four days, whether the vitamin A was given in an aqueous or oily medium. It seems quite clear that the duration of fecal collection was not long enough to include all the excretion of vitamin A by some of the children who had a relatively sluggish intestinal motility. These very high fecal vitamin A values indicate that the standard test dose of the vitamin is probably far higher than necessary.

IX. *Liver Vitamin A Content in a Child Dying of Acute Rheumatic Fever and Rheumatic Heart Disease.*

J. S., a 7-year-old girl, was admitted to the hospital in congestive heart failure and with a history of rheumatic fever of four months' duration. For two weeks prior to admission she received cortisone, 400 mg. daily. Physical examination on admission showed evidence of severe carditis with marked cardiac enlargement, hepatomegaly, and peripheral edema. Her body temperature was 100.5 F. In addition to the general supportive measures and the treatment of heart failure, the girl was given cortisone, varying from 100 to 50 mg. daily, for another 14 days and corticotropin for one day before her death. She received no supplementary vitamin A preparations after admission to the hospital. Her serum vitamin A was 79 γ per 100 ml. and her carotene, 90 γ per 100 ml. on the second day after admission. She died 21 days later. Autopsy showed rheumatic pancarditis and passive congestion. The value of the liver vitamin A content was 20,300 γ per 100 gm. This is much higher than the median of 3,940 γ per 100 gm., reported for 12 healthy children between 4 months and 12 years of age, who died in accidents.[14]

X. *Liver Function and Regulatory Mechanisms of Serum Vitamin A Levels.*—It has long been recognized that the serum vitamin A level does not necessarily reflect the vitamin A concentration in liver tissue.‡ Nevertheless, the change in the serum vitamin A level seems to be a reliable indicator of hepatic function. Abnormally low values of plasma vitamin A have been found in various types of hepatic diseases.§ In our study, the serum vitamin A levels varied inversely with the degree of hepatic congestion in cardiac decompensation. These findings suggest that the decrease of vitamin A level in acute rheumatic fever also results from hepatic dys-

† References 18 and 22.

‡ References 8-9.

§ References 8 and 23.

function. Alteration of serum proteins as determined by electrophoresis, which is considered as one of the measures of liver function, is also observed in acute rheumatic fever.[24]

The question arises as to the pathogenesis of this hepatic dysfunction in the early stages of rheumatic fever.

The rise of serum vitamin A levels during the acute stage of rheumatic fever, after the administration of corticotropin or cortisone, certainly cannot be due to an increase of dietary intake alone. It has been demonstrated that human beings have a tendency to maintain a constant plasma vitamin A level, even when large doses of the vitamin were given for a considerable length of time.[25] Alcohol and epinephrine also were found to mobilize serum vitamin A from the reserve.‖ It seems as though these substances, alcohol, epinephrine, corticotropin, and cortisone, work through the same channel of the sympatheticoadrenal mechanism in controlling the release of vitamin A in animals during stress. Thyroid and testosterone were found to exert an influence on the metabolism of vitamin A.¶ But up to the present time, very little is known concerning the over-all picture of the body regulatory mechanism of the vitamin A and carotene metabolism in health and sickness. In acute rheumatic fever, as well as in other febrile diseases, probably the increased utilization of vitamin A and a blockage of enzymatic activity of the liver cells accounts for the sudden drop of the serum vitamin A levels. Whether or not this blockage of enzymatic activity is related to a readjustment of some unknown endocrinological mechanism can only be determined by further investigations.

CONCLUSIONS AND SUMMARY

It is concluded from this study that the diet for the child with rheumatic fever should be supplemented with 3,000 to 5,000 I. U. of vitamin A. During the acute stage, the need for supplementation is greater, as frequently the child's nutritional intake is limited during this phase of the disease. High normal values were observed more consistently during the subacute and inactive stages of the disease when vitamin A intake was ample. The aqueous preparation was found to be absorbed more rapidly. No indication was found for giving large amounts of vitamin A, and it is advisable to keep in mind that fat-soluble vitamins are stored in the body and that large amounts taken over a period of time can be toxic.

The serum vitamin A level of rheumatic children is found to be decreased under the following conditions: (*a*) during the acute and early subacute stages of the disease, (*b*) in patients with severe cardiac damage with passive congestion of the liver, (*c*) during intercurrent upper respiratory infections, (*d*) in patients with acute exacerbation of rheumatic processes, and (*e*) in patients with an inadequate vitamin A and carotene intake of some duration.

Corticotropin and cortisone profoundly affect the levels of serum vitamin A and carotene during the various stages of active rheumatic fever.

With a few exceptions, vitamin A, either in aqueous or oily medium, was well absorbed by children in varying stages of rheumatic fever.

‖ References 26-27.

¶ References 28-29.

There is no evidence that children with rheumatic fever have a higher vitamin A requirement than normal children.

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STUDIES ON THE UNDERNOURISHED CHILD

XII. Anemia in Malnourished Children

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SINCE Galesesio and Slantineano, in 1909, reported moderate anemia in patients affected with pellagra,[1] the great majority of authors who have studied this problem agree on the presence of anemia in persons suffering from malnutrition.

From the morphologic point of view, anemias have been reported as macrocytic, microcytic, and dimorphic, and, in relation with infantile malnutrition, the morphologic type most frequently found has been the normochromic normocytic.[2]

Morphologic classification of anemias, as determined by measurement of factors such as the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular concentration of hemoglobin and by the examination of blood slides, has a great value, especially in the study and nature of erythropoiesis, but such morphologic classification is of less importance in the investigation of the etiologic and pathologic factors involved in the production of anemias.

From a review of works on anemias in undernourished children, two clear facts may be pointed out: first, anemia is always of medium intensity, and second, constant disturbances in erythropoiesis are found only exceptionally.

Considering that in malnutrition the morphologic type of anemia most frequently found is the normochromic-normocytic and that the most characteristic finding is the increase of extracellular water, we thought, as a hypothesis, that in undernourished patients the increase of blood volume * could explain the appearance of the anemia in its most usual morphologic type and could also account for the poor response of this anemia to so-called specific hematopoietic agents.

The aim of this paper is to report the red-cell pictures found in patients affected with noncomplicated malnutrition and the influence that blood volume has on those pictures.

METHODS

Two cubic centimeters of blood was drawn by venous puncture without stasis and placed in a test tube containing a mixture of ammonium and sodium oxalates. Samples were taken from this for determining the hematocrit, the amount of hemoglobin, and the number of red cells.

From the Nutrition Department of the Hospital Infantil.

* References 3-5.

1. Hematocrit.—Wintrobe's tubes were used, and samples were centrifuged at 3,000 rpm for 30 minutes.

2. Hemoglobin.—The hemoglobin was determined by the oxyhemoglobin [26] method, using Evelyn's photoelectric colorimeter.

3. Erythrocytes.—The erythrocytes were counted, using the Neubauer ruling, according to routine methods.

With the above data, calculations were made for mean corpuscular volume and mean corpuscular hemoglobin.

4. Blood Volume.—The blood volume was determined by Gibson and Evans' method of injecting a solution of Evans blue dye, T—1824, and drawing a sample of blood 10 minutes later; Gregersen's [6] correction was not made, since it was not done when determining values for healthy preschool children.

Theoretical blood volume was figured for the children under study by considering their actual weights independently of their ages and heights, according to the following formula [7]:

$$\text{Blood volume in cubic centimeters} = (120.50 \times \text{weight}) - 239.56$$

5. Proteins.—Total proteins and their fractions were determined according to the technique already described.[8]

Robles Gil and González have pointed out that macrocytosis occurs in plateaus; this fact must be kept in mind when judging the normality of the mean corpuscular volume in the cases under study. Mugrage and Andresen [9] have reported that the figures for hematocrit, hemoglobin, and erythrocytes remain constant after the second year of life; such values are almost identical with those found in adults.

For the above reasons, the figures for hematocrit, hemoglobin, and erythrocytes obtained by Mena Brito [10] are considered normal, and for mean corpuscular volume and hemoglobin, Robles Gil and González [11] figures.

Once values for hematocrit, hemoglobin in grams per 100 cc., and erythrocytes per cubic millimeter were found, calculations for total circulating values were obtained by multiplying blood-volume figures by hte number of erythrocytes and by the amount of hemoglobin.

In the same way, theoretical values were obtained, considering the blood volume which the patient should have had for his weight at the moment he was being studied.

Statistical Methods.—From each series of determinations, the arithmetic mean, the standard deviation, and the standard error of the mean were obtained.

Series were compared to each other according to the following formula:

$$C_1 = \frac{\text{Dif.}}{\text{Sigma Dif.}}$$

"Dif." represents the difference of the means and "Sigma dif." is the standard error of the difference.

As in this study we intended to detect differences, although small, we considered a value above two for C_1 as statistically significant.

MATERIAL

Our material included 51 patients from the Nutrition Department of the Hospital Infantil. There were 24 females and 27 males. Ages fluctuated between 9 months and 7 years. The distribution by ages appears in Table 1.

The patients all suffered from malnutrition; the degree of malnutrition is shown in Table 2.

The frequency of clinical edema and of the skin lesions of "pellagra" in the 51 cases studied is shown in Table 3. The results of parasitoscopic examination and stool culture are shown in Tables 4 and 5.

In short, it may be said that our material was made up of children showing the characteristic pictures of malnutrition due to chronic underfeeding, complicated in some instances with parasitosis or infections.

TABLE 1.—*Frequency of Ages in Fifty-One Cases*

Age, Yr.	No. of Cases
6/12-1	2
1 1/12-1 6/12	11
1 7/12-2	13
2 1/12-2 6/12	4
2 7/12-3	11
3 1/12-3 6/12	0
3 7/12-4	6
4 1/12-4 6/12	1
4 7/12-5	1
6	1
7	1

TABLE 2.—*Frequency of Degree of Malnutrition*

Degree of Malnutrition	No. of Cases
First-degree	1
Second-degree	19
Third-degree	31

TABLE 3.—*Frequency of Edema and Skin Lesions of Pellagra*

Pathologic Signs	No. of Cases
Edema	34
Skin lesions of pellagra	49

TABLE 4.—*Positive Stool Cultures*

Germ Isolated	No. of Cases
Shigella flexneri	5
Salmonella sp. (type derby)	3
Pseudomonas aeruginosa	2
Salmonella Group C_3	2

TABLE 5.—*Types of Parasites Found in Stool Examination*

Parasites	No. of Cases
Giardia	5
Ascaris	2
Uncinaria	1
Oxyuris	1
Isospora hominis	1
Endolimax	1
Ameba	1

TABLE 6.—*Mean Values for Hemoglobin and Erythrocytes in Fifty-One Cases*

Hgb., Gm./100 Cc.		Erythrocytes/Cu. Mm.	
M	S. D.	M	S. D.
9.26	2.95	3,511,765	927,361

TABLE 7.—*Frequency of Diverse Morphologic Types of Anemia*

Type	No. of Cases
Normocytic-normochromic	17
Normocytic-hypochromic	10
Microcytic-normochromic	4
Macrocytic-hyperchromic	4
Macrocytic-normochromic	3
Microcytic-hypochromic	1

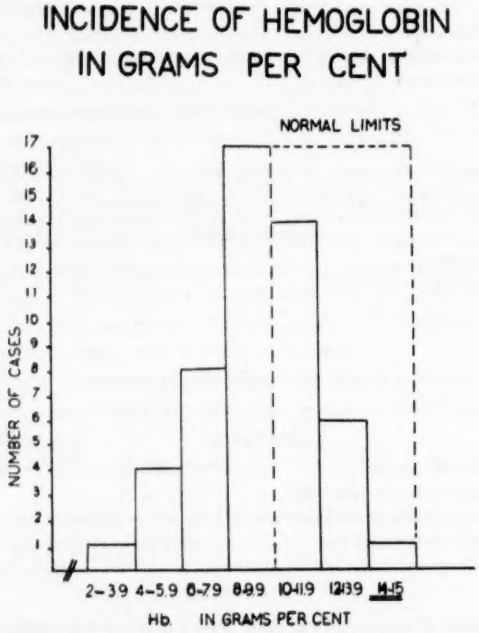

Chart 1

RESULTS

Values found for hemoglobin in grams per 100 cc. and erythrocytes per cubic millimeter are shown in Table 6, where the arithmetic mean (M), and the standard deviation (S. D.), are also listed. Of our 51 cases, 39 were anemic and the rest showed no anemia. The types found and their classification are shown in Table 7. The results are shown in Charts 1, 2, 3, and 4.

INCIDENCE OF ERYTHROCYTES PER CUBIC MILLIMETER

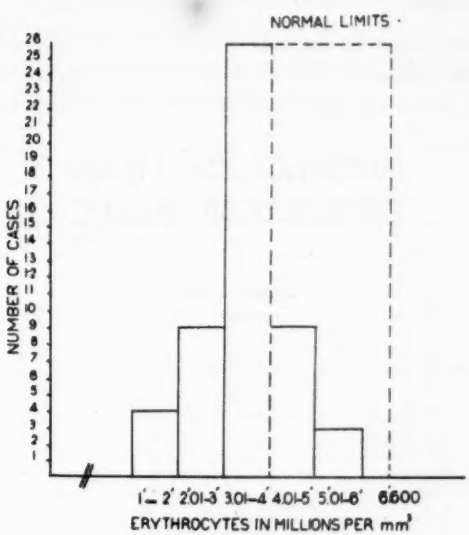

Chart 2

INCIDENCE OF MEAN CORPUSCULAR HEMOGLOBIN

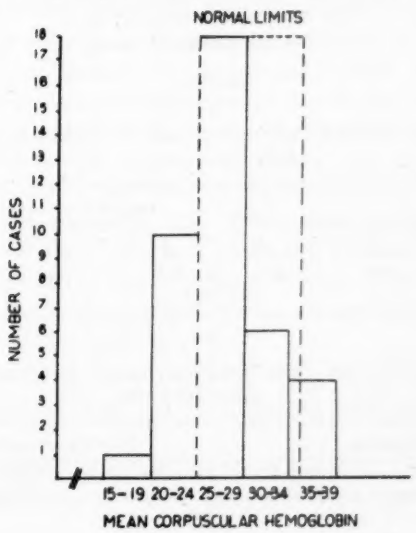

Chart 3

Tables 8 and 9 show the figures for total hemoglobin and total circulating erythrocytes; these figures are compared to the theoretical figures that would correspond to actual weight which, as has been pointed out, is the weight at the time the study was initiated.

As stated before, in our 51 cases there were 12 with figures for red cells above 4,000,000 per cubic millimeter, and thinking that these figures would be in favor of the fact that no statistically significant difference was found between erythrocytes

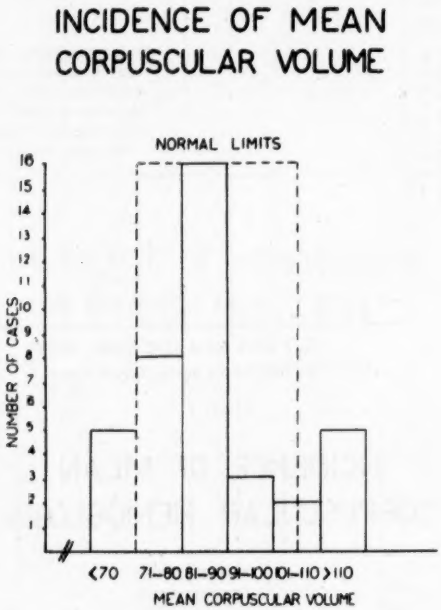

Chart 4

TABLE 8.—*Comparison of Real and Theoretical Figures for Total Circulating Hemoglobin in Fifty-One Cases*

Total Hgb., Gm./100 Cc.			Theoretical Figures for Total Hgb., Gm./100 Cc.		
M	S. D.	S. E.	M	S. D.	S. E.
86.26	30.47	4.3	82.46	43.15	6.04

$C_1 = 0.027$

TABLE 9.—*Comparison of Real and Theoretical Figures for Total Circulating Erythrocytes in Fifty-One Cases*

Total Erythrocytes			Total Theoretical Erythrocytes		
M	S. D.	S. E.	M	S. D.	S. E.
3,081,193	1,402,000	196,358	3,260,469	1,552,000	217,367

$C_1 = 0.63$

and total hemoglobin in the groups compared, we studied the remaining 39 cases separately. However, our conclusions were not modified. Tables 10 and 11 show the results.

As it may be seen, no significant statistical difference was found, since C_1 was 0.87 for hemoglobin and 0.45 for erythrocytes.

Charts 5 and 6 show the relationship found between blood volume and erythrocytes and between blood volume and hemoglobin.

TABLE 10.—*Comparison of Real and Theoretical Figures for Total Circulating Hemoglobin in Thirty-Nine Cases*

Total Hgb., Gm./100 Cc.			Theoretical Total Hgb., Gm./100 Cc.		
M	S. D.	S. E.	M	S. D.	S. E.
81.61	31.05	4.98	88.44	37.37	5.98

$C_1 = 0.87$

TABLE 11.—*Comparison of Real and Theoretical Figures for Total Circulating Erythrocytes in Thirty-Nine Cases*

Total Erythrocytes			Total Theoretical Erythrocytes		
M	S. D.	S. E.	M	S. D.	S. E.
2,972,978	1,552,823	24,800	3,475,456	1,561,475	250,200

$C_1 = 0.45$

COMMENT

About fifty years ago, Schlesinger stated that moderate anemia in the undernourished child is fundamentally caused by a "dilution of plasma,"[12] but this theory was ignored by almost all workers who studied the problem later. Probably, Chang, who in 1932 [13] erroneously reported a decrease of blood volume in seven cases of starvation edema, contributed to the neglect of Schlesinger's concept.

Thus Altmann and Murray [2] concluded that anemia in the undernourished African child is almost always moderate, and normochromic-normocytic in type, but these authors, taking into account Chang's report, excluded an increased blood volume from the factors that might explain anemia. The results of Keys' and his co-workers' investigations [14] and those of Beattie, Herbert, and Bell, in adults,[15] confirmed that both extracellular fluid (thiocyanate space) and plasma volume, calculated in grams per kilogram of body weight, are increased in malnutrition. This fact has been emphasized by other workers † to such a degree that it appears as one of the most predominant characteristics in malnutrition.[18] In our own experience, we have obtained the same result.[19]

The fact that the blood volume increased during the first days of recovery does not necessarily mean, as Altman and his co-workers supposed, that it had decreased beforehand.

Studies on the behavior of extracellular fluid during the recovery syndrome show that plasma and blood volumes are increased per kilogram of body weight and that

† References 16-17.

such an increase is greater at the beginning of recovery, causing in this manner a greater dilution that appears responsible for the fall of hematocrit levels, hemoglobin, and erythrocytes, as reported by Altman and by Walters and his co-workers.[20]

From the results obtained in our work, we may deduce with other authors ‡ that noncomplicated malnutrition is associated with a moderate anemia. This fact is

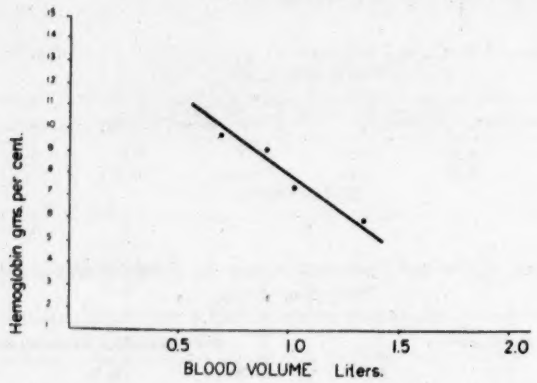

Chart 5.—Correlation between blood volume and hemoglobin.

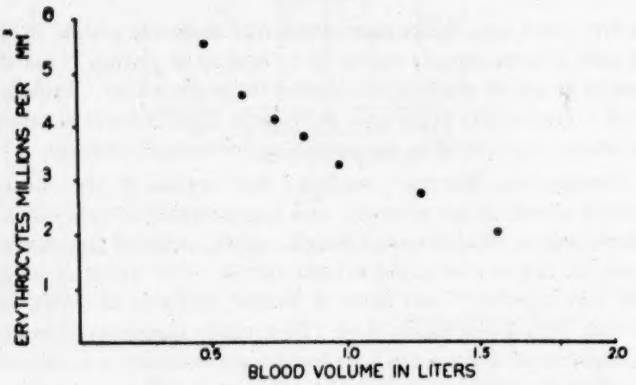

Chart 6.—Correlation between blood volume and erythrocytes per cubic millimeter.

shown in Charts 1 and 2, where the most frequent figure for red cells is between 3,000,000 and 4,000,000 and for hemoglobin, between 9 and 11 gm.

According to the morphologic classification of anemias, our results proved that the most frequent type is the normochromic-normocytic. Next in frequency is the hypochromic-normocytic type.

‡ References 1-2.

If we consider this anemia according to the number of red cells per cubic millimeter and the grams per 100 cc. of hemoglobin, we may see that it does not hold true when considering total circulating values because of the increase in blood volume found in the undernourished. This shows that the normal child and the undernourished have the same number of red cells, providing the weight is the same in both. Routine techniques show smaller amounts of cells because they are found in a diluted form. Charts 5 and 6 illustrate this idea more clearly; it may be seen that figures under discussion for our 51 cases increased as blood volume decreased.

From the above, we believe that anemia in infantile malnutrition is less marked than would appear when using routine techniques and that in some cases there is no anemia at all.

In malnutrition complicated with a serious pathologic process, we have seen the figures for hemoglobin and erythrocytes divert from the mean figures. This is due to the fact that a serious process other than malnutrition is in itself capable of producing anemia, much more so when a process acts on a child affected with malnutrition.

On the other hand, there are authors who claim that in plain malnutrition, erythropoiesis remains unchanged for a longer time than other functions, since hemoglobin, being an intracellular component, is less vulnerable to metabolic demands than serum proteins.[21] Robscheit-Robbins and co-workers have shown that an organism that has lost its hemoglobin may manufacture it from its own proteins.[22] Also Whipple, experimenting with undernourished and anemic dogs, proved that proteins from their diets are used, primarily, in the manufacture of hemoglobin and, secondarily, to provide plasma proteins.[23]

It is interesting to point out that in our cases there was no correlation between serum proteins and hemoglobin figures, that is, it was not proved that a greater protein deficiency (characterized by a greater decrease of serum albumin) would correspond to a more severe anemia. This finding would be in opposition to the ideas of those who have supposed protein deficiency to be the etiology of malnutrition anemia.§

The concept that seems to be inferred from our work is that malnutrition, when causing an increase of blood volume, makes for a decrease in hemoglobin figures and in erythrocytes per unit of volume in such a manner that, even if these elements may be influenced directly by the nutritional process, their fall is more apparent because of this dilution factor. Moreover, studies on the recovery of the undernourished child treated exclusively with dietetic measures without adding commercial specialties [25] have lead us to consider that anemia, as studied here, is nothing but another unspecific syndrome found in malnutrition and that like other anatomicopathological findings (disorders of the skin, decreased enzymatic activities of duodenal contents, changes in the hair, etc.), it is cured when the organism is supplied with those energy-producing and plastic materials needed for its development and growth.

§ References 2 and 24.

SUMMARY

This paper is based on the results obtained from the study of 51 undernourished children in whom determinations were made of hemoglobin and erythrocytes in relation to blood volume in order to find the frequency and type of anemia they showed.

Figures for hemoglobin and erythrocytes, determined by the usual techniques, show there is a moderate anemia associated with infantile malnutrition.

From the morphologic point of view, normochromic-normocytic anemia was the type most frequently found.

Due to an increase of plasma volume, as found in these patients, their anemia must be considered as a hypervolemia.

In those cases of severe anemia where figures obtained were not in relation to a given blood volume, there were additional pathologic processes other than malnutrition which accentuated the intensity of the anemia.

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STUDIES ON THE UNDERNOURISHED CHILD

XIII. Treatment of Third-Degree Malnutrition Without Commercial Vitamins

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AFTER having treated a large number of cases affected with third-degree malnutrition, where so-called deficiency lesions were seen, such as edema, pellegra, ariboflavinosis, xerosis, various bone lesions, changes in color and texture of the hair, follicular hyperkeratosis, perifolliculitis, emotional changes, psychic deviations, backwardness, persistent anorexia, muscular flaccidity, and autophagia in varying degrees, all cured only by giving adequate amounts both in quantity and in quality of nutritional elements and, specifically, without the addition of commercial vitamins, we thought it interesting to report these facts.

Actually, for several years we treated children complaining of serious malnutrition according to classic ideas, adding all kinds of vitamin preparations to adequate diets, but the favorable progress in many cases which were treated differently has made us change our older therapeutic methods.

The results obtained following our new ideas in treating the above-named disorders are the reason for this preliminary report.

MATERIAL

A study was made on 373 children admitted to the Nutrition Department of the Hospital Infantil with the diagnosis of malnutrition caused by chronic underfeeding and treated exclusively with full diets; blood or plasma transfusions were given when necessary.

Of these children, 48% were males and 52%, females.

Ages were distributed as shown in Table 1. The distribution of the percentage of body weight, compared to the "average theoretical weight" for a particular age is shown in Table 2.

Edema was found in 71% of the cases; the incidence of skin lesions varied whether edema was present or not, as may be seen in Table 3. Other important data found during the study of the conditions on admission are shown in Table 4. The parasites found in 28% of the cases are listed in Table 5. Table 6 shows the results of the stool cultures obtained.

The study of the long bones showed the lesions of chronic malnutrition, with some evidences of what has been called hypovitaminosis C in 60% of the cases.

On admission, the group showed hypoalbuminemia in every instance and hypoproteinemia in 87% of the cases, with mean figures of 1.83 gm. of albumin per 100 cc. of serum, and 4.65 gm. of total proteins per 100 cc. of serum.

From the Nutrition Department of the Hospital Infantil.

TABLE 1.—*Frequency of Ages in 200 Cases*

Age, Mo.	% of Cases
Under 12	7.74
12-23	43.80
24-35	25.07
36-47	12.26
48-59	4.33
60-71	4.17
72-83	1.87
84-95	0.76

Mean age, 31 ± 17.

TABLE 2.—*Distribution of Weight Compared to Normal*

% of Average Theoretical Weight	% of Cases
31-40	10.50
41-50	33.75
51-60	37.55
61-70	14.70
71-80	3.50

Mean, 52 ± 10%.

Mean height, 89% ± of the average theoretical height for a given age.

TABLE 3.—*Signs and Symptoms Found on Admission*

Type of Lesion	Patients Without Edema, %	Patients With Edema, %
Dry hyperchromic nondesquamative skin	90	94
Very dry skin with hyperchromic lesions, which give it a mosaic aspect	38	46
Follicular hyperkeratosis	20	26
Hyperkeratosis palmaris et plantaris	48	37
Fissures of the skin	3	8
Seborrheic skin	42	49
Pellagrose erythema	13	47
Acute pellagrose dermatitis	18	40
Dyskeratosic hyperchromic lesions	50	83
Desquamative lesions, in large flaps	8	21
Desquamative lesions, in small flaps	13	37
Postdesquamative hypochromic skin	15	26
Hyperchromic skin along capillary circulation	1.4	7.89
Crusty lesions, suggestive of being postpurpuric	6	11
Purpuric lesions	24	28
Perifolliculitis	1.4	11
Coldness and cyanosis predominating in distal ends of extremities	62	82
Marbleization of the skin	11	18
Telangiectasis	1.4	5.9
Gangrenous lesions and eschars	11	18
Hypertrichosis	24	20
Sign of the "wet cloth"	27	11
Collateral abdominal venous circulation	6	7

TABLE 4.—*Lesions Found on Admission, not Directly Due to Malnutrition*

Clinical Findings	% of Cases
Dehydration	56
Diarrhea	70
Vomiting	39
Hyperthermia	32
Hypothermia	31
Parenteral infections	51
Positive syphilitic reactions	2.6
Positive Manfoux	4

TABLE 5.—*Parasites Found in Twenty-Eight per Cent of the Cases Studied*

Type of Parasite	% Found
Giardia lamblia	13.0
Ascaris lumbricoides	7.7
Endolimax nana	3.1
Trichuris trichiura	2.8
Endamoeba histolytica	1.9
Endamoeba coli	1.9
Necator americanus	1.2
Enterobius vermicularis	1.2
Hymenolepis nana	0.9
Trichomonas hominis	0.3

TABLE 6.—*Stool Cultures*

Germ Isolated	%
Without pathological germ	72
Shigella	14.3
Salmonella	9.4
Other suppositively pathological germs	4.3

TABLE 7.—*Frequency Figures of Erythrocytes per Cubic Millimeter*

Erythrocytes	% of Cases
1,000,000-1,900,000	3.3
2,000,000-2,900,000	9.5
3,000,000-3,900,000	43.5
4,000,000-4,900,000	34.2
5,000,000-5,900,000	9.5

TABLE 8.—*Frequency of Hemoglobin Figures in Grams per One Hundred Cubic Centimeters*

Hemoglobin, Gm./100 Cc.	% of Cases
4- 5	3.3
6- 7	6.2
8- 9	18.7
10-11	50
12-13	15.6
14-15	6.2

The figures for hemoglobin were under 13 gm. in 93.7% of the blood cell counts obtained on admission, and the red cell count was under 4,000,000 per cubic millimeter in 56.8% of the cases. Frequency curves are shown in Tables 7 and 8.

The great majority of the cases showed marked anorexia. Good appetite was seen in only 8.7% of the cases.

Table 9 is a summary of some complementary data obtained from these children.

METHODS

When necessary, various solutions were given to correct electrolyte disturbances, and as soon as possible (from 10 to 18 hours later), half-skimmed-lactic-acid-milk formulas were begun at the rate of 60 to 80 Cal. per kilogram of body weight per day, changing rapidly to larger amounts (80 to 100 Cal. per kilogram of body weight per day). Still later, whole-lactic-acid-milk formulas with the addition of 10% corn syrup were given freely. Thus, from 100 to 150 Cal. per kilogram of body weight were ingested.

As soon as possible, semisolid foods, such as gelatin, banana, bread, "tortilla," mashed liver, hot sauce, ground meat, beans, and crackers, were added. Generally speaking, it may be said that one or two weeks after admission, these patients were taking routine diets ad libitum. Some older children were on this self-demand regimen from the time of their admission. During the first days it was rarely necessary to use tube-feeding methods.

TABLE 9.—*Complementary Data*

Classification	% of Cases
Females	52
Males	48
First-born	3.3
With past histories of diarrhea	56
With past histories of parenteral infection	47
Sufficient feeding for 7 ± 3 mo.	
Prolonged underfeeding for 24 ± 15 mo., (representing 72 ± 15% of the children's ages).	
Past history of diarrhea of 6 ± 4 mo. duration.	
Normal psychomotor development until 10 ± 7 mo. of age.	

During the first two weeks, blood transfusions were given in 65% of the cases, while 35% of the patients definitely received no other treatment than adequate diets.

The criterion followed in giving blood or plasma transfusions was the presence of massive edema or an excessive delay in gaining weight.

The total transfusion given was less than 60 cc. per kilogram of body weight in 57% of the cases, from 60 to 120 cc. in 19% of the cases, and from 120 to 180 cc. in 19% of the cases; only 5% of the cases received a larger dose. The average total dose in the children treated with transfusions was 76 cc. ±55 cc. per kilogram of body weight.

The children remained in the hospital until they showed (*a*) definite and permanent improvement of appetite, (*b*) a progressive increase in the weight curve and a significant gain compared to the weight on admission, (*c*) the disappearance of edema, (*d*) a clinical healing of the skin lesions, (*e*) normal levels of serum albumin and total serum proteins, and (*f*) obvious psychic and emotional manifestations of well-being.

Eventually, a few patients remained in the hospital for a longer time in order that the nutritional-recovery syndrome [1] which they all presented could be studied.

RESULTS

(*a*) *Appetite.*—From the clinical point of view, an improvement of the appetite could be judged by observing the growing interest the patients showed for all foods and the consumption of them, as seen in Chart 1.

(*b*) *Weight Curve.*—After the initial loss caused by the disappearance of edema, a constant increase in weight was obtained. The mean figures shown in Table 10 are represented in Chart 2.

The difference between the weights on admission and those obtained at the end of six weeks of treatment was statistically significant ($t = 4.95$).

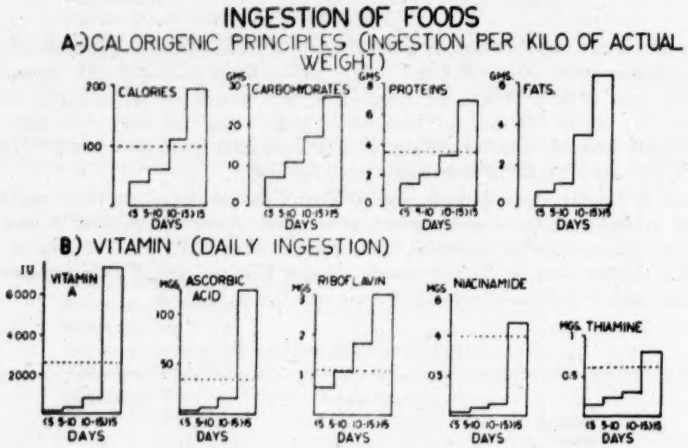

Chart 1

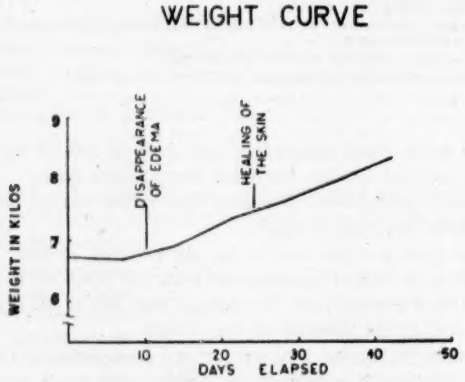

Chart 2

TABLE 10.—*Mean Weight for the Group Studied*

Week	Weight, Gm.
Admission	6,766
First	6,715
Second	6,984
Third	7,373
Fourth	7,626
Fifth	7,975
Sixth	8,236

TABLE 11.—*Modifications of Serum Proteins (Mean Values)*

Fraction	Admission and First 9 Days, Gm./100 Cc.	10-19 Days, Gm./100 Cc.	20-29 Days, Gm./100 Cc.	30-39 Days, Gm./100 Cc.	40-49 Days, Gm./100 Cc.
Albumin	1.83	2.37	2.82	3.15	3.52
Globulin	2.86	3.44	3.55	3.83	3.66
Total proteins	4.65	5.77	6.54	6.96	7.13
Alpha globulin	0.65	0.90	1.08	1.05	1.10
Beta globulin	0.74	0.81	0.82	0.95	0.61
Gamma globulin	1.53	1.74	1.91	1.92	1.92

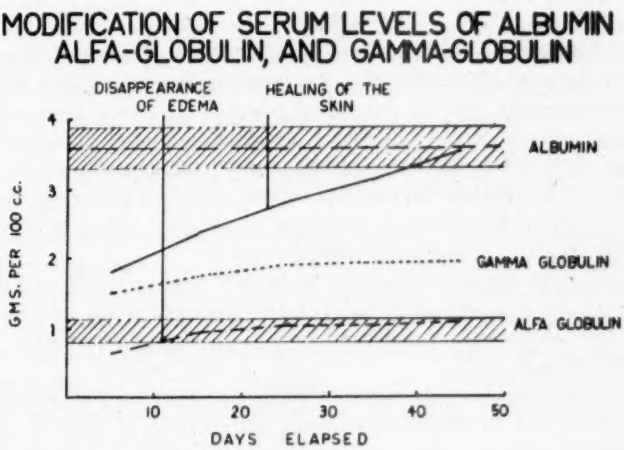

Chart 3

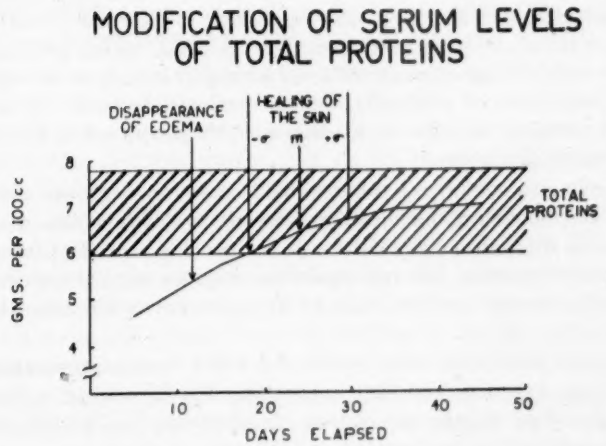

Chart 4

(*c*) *Disappearance of Edema.*—Clinically, edema disappeared in 11 ± 4 days. In none of the cases that had had edema did it disappear before the fifth day. It disappeared between the 6th and the 10th days in 44% of the cases and between the 11th and the 15th days in 48% of the cases. Finally, in 8% of the cases edema disappeared between the 16th and the 20th days.

(*d*) *Clinical Healing of Skin Lesions.*—The skin lesions disappeared by the 24th ± 6 days, having at the end the thin, fine, transparent, and elastic aspect peculiar to healing.

(*e*) *Modifications of Serum Proteins.*—Serial determinations of serum proteins were done. Table 11 and Charts 3 and 4 present the changes observed.

COMMENT

Concept of Malnutrition.—The study of these patients together with their clinical evolution demonstrates still further that the term "malnutrition" is a word that simplifies, advantageously, the old and varied nomenclature, such as hypothrepsia, athrepsia, hypotrophia, dystrophia, atrophia, decomposition, and pellegra, and the modern names, such as kwashiorkor, dysontia, and hypoproteinosis, since all these names simply refer to different degrees and aspects of the same disease, where the pathogenesis is always the deficient utilization of adequate amounts of essential nutrients by the organism, whatever the etiology may be.

What we call third-degree malnutrition is the final stage of nutritional deficiencies or privations and of severe autophagia, evidently present in the subjects of this study, where the mean weight was around 50% of the average theoretical weight, considered for each age.

The human body reaches this situation when the organism has exhausted its nutritional reserves and all the plastic elements within reach in order to maintain a minimal metabolic balance; in the group under study this took place after a serious underfeeding that lasted for two years, three-fourths of the time "lived" by these patients.

When the minimal metabolic equilibrium is broken, different clinical stages of advanced malnutrition, such as edema, xerosis, changes in color and texture of the hair, apathy, emotional distortion, and intractable anorexia, appear gradually and successively or suddenly and violently. Also, an incapacity is obvious for digestion, absorption, or utilization of foodstuffs, due to serious deficiencies of duodenal enzymes * and, probably, also due to fundamental changes in cell structures and their internal enzymatic systems.

In chronic malnutrition due to insufficient food intake, the organism shows this serious picture simply because the nutritious elements needed for tissue repair, for its reproduction, and for the work of the cells are not available. This means that adequate amounts of proteins, fats, carbohydrates, vitamins, salts, and water, all of which are found in normal and well-balanced diets, are not at the disposal of the organism.

From the minute description of the condition in which these patients arrived and from their previous infections and dietetic histories, it is easy to get a clear idea of the serious pathologic picture seen in them on admission. Undoubtedly the subjects chosen are sufficient for our purpose, and the group is significant.

* References 2-4.

The metabolic equilibrium to which we have been referring was broken because other secondary causes were added to the primary cause of malnutrition (chronic undernourishment).

Treatment Without Commercial Vitamins.—If the primary cause for these serious deficiency pictures, not including infections or congenital malformations, is the poor or nonexistent supply of substances from the nutritional complex under discussion, logically, the most reasonable treatment for such a condition is to furnish the organism in a complete and balanced manner with the whole group of lacking elements, providing for the exhausted tissues all those foodstuffs which have been lacking for such long periods of time.

Offhand, it would be an obvious mistake to try to treat a patient affected with nutritional deficiencies, autophagia, pellagra, edema, xerosis, or kwashiorkor with large doses of the single nutritional complex element which we suppose is lacking, for instance, large doses of carbohydrates, salts, nicotinic acid, ascorbic acid, vitamin A, fats, or proteins, without taking into account the biologic synergy of the remaining elements. We cannot forget the inviolable principle of physiology and nutrition which states that the diet must be well balanced and complete in order to be conveniently utilized by the tissues.

As has already been said, in the group analyzed here the fundamental treatment was a generous diet following a regimen of self-demand and, secondarily, blood or plasma transfusions. As a result of this treatment, after six weeks there was such an increase in weight that, using 100% as a base for the minimal weight recorded after the disappearance of edema (in the absence of dehydration), the weight at the sixth week was 129% ± 12. A healthy and normal child of the same age as the mean for our cases (2½ years) succeeds in gaining an equivalent weight at the end of 18 months, that is, at the age of 4 years.

Such a remarkable gain in body weight was possible because of a spontaneous change of appetite. The basis for this modification was probably the emotional adjustment obtained by our patients, rather than a substantial change in digestive secretions, so precarious and faulty in the undernourished child, and, apparently, was without correlation with an interest in or indifference to food.

Skin Lesions.—Skin lesions in malnutrition were followed, as usual, by desquamation. The skin was considered clinically healed in a rather short time (24 ± 6 days). The appearance of the new skin was peculiar to that seen in the period of recovery,[1] thin, fine, transparent, and elastic. It frequently showed the residual dichromic alterations which take such a long time to heal.

We do not think the extension or severity of skin lesions may be a guide for prognosis or healing. Although the reasons for this report are different, it may be said here that the outlook in these patients depends on factors which directly affect the tissular capacity for making use of the nutrients, factors such as dehydration, saline unbalance and depletion, more or less serious infections, diarrhea, and condition of the bone marrow.

Nitrogen-balance studies help in the estimation of the capacity of the cells to make use of the nutrients; when the balance is positive, there is reason to speak of improvement and recovery. But when such studies cannot be carried out, we have found that a determination of serum proteins is a laboratory procedure which, if

practiced in series, may help in judging recovery in malnutrition, since we have shown, among other characteristics,† that hypoalbuminemia is always present.

When malnutrition reaches extreme degrees, we see other phenomena, such as total hypoproteinemia, a greater decrease of albumins, and a decrease of alpha globulin; these conditions allow or make way for the appearance of edema. Hypergammaglobulinemia may be seen when there are, in addition, infections or hepatic degeneration processes.

All the above-mentioned circumstances occurred in our group. Thus we obtained the pattern already described as peculiar to third-degree malnutrition, and, as shown in Charts 3 and 4, serum proteins changed during the study, following patterns already established for the nutritional-recovery syndrome.[1]

Thus, albumins reached figures of 2.37 gm. per 100 cc. on the 20th day, 5.83 gm. on the 30th, and 3.15 gm. on the 40th, only to become normal between the 40th and 49th days of treatment, while total proteins became normal by the 20th and 29th days.

Edema.—Edema disappeared, as shown in Chart 2, by the 11th ± 4 days, when albumins had reached a level of 2 gm. per 100 cc. and alpha globulins were within lower normal limits. It must be kept in mind that the skin lesions healed by the 24th ± 6 days, that is, at the same time that the total proteins reached lower normal limits but when the albumins were still far from reaching normal levels. In this observation may be found a new argument to sustain the view that neither the disappearance of edema, the clinical healing of skin lesions, nor the normalization of total proteins has a definite value in establishing the moment when recovery from third-degree malnutrition occurs.

Since the increase of blood volume has already been shown ‡ in third-degree malnutrition, we did not consider it important to do serial studies of hemoglobin and erythrocytes, which would have had no actual value if determinations of blood volume were not done simultaneously.

The frequency curve of hemoglobin and erythrocytes is in every way similar to that found in other work,[10] that is, a "dilution" of erythrocytes per unit of volume; this is characteristic of malnutrition and is not a fault of the liberation, formation, maturation, or saturation of these elements, except in those cases, as in one of ours, where a highly pressing extranutritional factor may be found, such as uncinariasis.

We believe the facts and observations presented here come to support the therapeutic criterion already stated in the sense that, if we give a complete and generous diet without the addition of commercial vitamins, the undernourished person responds immediately, providing there are no infections or any other cause that may interfere with digestion, absorption, or utilization of the nutritional complex and if the autophagia in the patient has not reached an irreversible state of tissular agony.

SUMMARY

In this preliminary report, we have only attempted to describe the facts which we observed, that is, a significant number of patients affected with third-degree malnutrition and with several other deficiency manifestations considered specific of

† References 1 and 5.

‡ References 7-9.

"vitamin deficiencies" who were cured of their lesions and who are fully recovering from their malnutrition without recourse to commercial vitamins.

After these observations, we are certain that seriously undernourished children with acute deficiency manifestations and advanced autophagia recover without the use of vitamins other than those found in a balanced diet and those which may be synthetized in their intestines. According to our experience, these sources were sufficient to correct the damage caused by the deficiency. Until now, in our studies, we have not found any cases that needed additional vitamins, whether injected or taken by mouth, to cure all their syndromes. Elements of the nutritional complex, given in a well-balanced diet and with opportunity, have been the basis of our therapeutics in our cases of malnutrition.

Stress is laid on the word malnutrition to designate a state of the organism which is caused by a deficient assimilation of adequate amounts of essential nutrients by tissue cells.

This term advantageously substitutes for the old nomenclature, which only points out signs or syndromes of different stages of the same disease.

The authors call third-degree malnutrition the final stage of nutritional deficiencies or privations, with autophagia.

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CORTICOTROPIN IN RHEUMATIC CARDITIS

Beneficial Effects of High Dosage and Short Duration in Acute Exacerbations of Chronic Rheumatic Carditis

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NEW YORK

SINCE 1949, when Hench [1] first reported his results of the treatment of rheumatic fever with an adrenal cortex hormone, many investigators have employed cortisone and corticotropin (ACTH) to relieve both the exudative and the proliferative phases of the disease.

A study of the results reported demonstrates conclusively that the exudative aspects of rheumatic fever have been satisfactorily controlled, and generally the response has been much greater and more rapid than had been obtained with salicylates. The drop to normal in temperature, the slowing of the heart rate, the diminution of the erythrocyte sedimentation rate, the elimination of pain, redness, and swelling of the joints, the return to normal of the prolonged P-R interval, the shortening of the Q-T, the suppression of abnormal antibody responses, and the reversal of the altered albumin-globulin ratio, all have responded uniformly well to hormone therapy.

Unfortunately, no one has been able to state unequivocally what effect hormone treatment has had on the proliferative phase of the disease. Barnes [2] suggested that suppression of the exudative aspects probably would lessen the tendency to scarring and valve injury. Dorfman [3] pointed out that only a long-range study with adequate controls would be of value in determining the desired answers.

Wilson [4] believed that early recognition at the onset of the initial attack of rheumatic fever and prompt treatment could successfully abort the exudative phase and thereby lessen the likelihood of cardiac damage. Her chief criterion was the return to normal size of an enlarged heart as observed on fluoroscopy. On the other hand, McEwen [5] believed that therapy must be maintained during the entire course of the active stage, somewhere between six weeks and three months, otherwise there would be a recrudescence of the rheumatic process. Massell [6] and Kuttner [7] have observed a satisfactory response in severe cases, and Adams [8] also indicated beneficial effects during the exudative phase of rheumatic fever.

A review of the available literature, excluding a number of individually treated cases, reveals an interesting aspect. There has been little uniformity in dosage. Both Massell and Kuttner have established certain standards for the use of both cortisone and corticotropin, requiring prolonged administration with progressively

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diminishing doses over a period of 6 to 8 weeks, and Massell recently has prolonged treatment to 16 weeks. Barnes, with somewhat smaller doses, concluded that his dosages were probably inadequate.

This lack of uniformity existed when the first cases of rheumatic fever were treated at the Morrisania City Hospital, in 1950. The mild attacks responded well to the small doses then in use. The severe cases either developed recrudescences or, at least, manifested rebound phenomena which were interpreted as flareups, when the treatment was stopped. Late in 1950, a moderately severe case of rheumatic carditis in a 6-year-old boy with mitral regurgitation and stenosis and aortic insufficiency was treated with 200 mg. of corticotropin daily, with the hope that the larger dose would be more effective in shortening the rheumatic activity, and, more significantly, might so alter the "antigen-antibody" reaction that the ultimate danger of further scarring would be prevented. This child's response was gratifying in that no rebound phenomena were noted after 14 days of this treatment (50 mg. every six hours). Also significant was the absence of undesirable side-effects. Emboldened by this success, we decided to treat a series of cases of proved rheumatic carditis with even larger doses, using 300 mg. per day of corticotropin for a period of 14 to 18 days. Our purpose was to determine whether these larger doses would be more effective in controlling the rheumatic process, particularly the proliferative phase, and whether they would fulfill Massell and Warren's [9] criteria for the ideal dosage: (1) maximum suppression in the shortest time, (2) minimum untoward effects, and (3) no rebound or a minimal one which recedes spontaneously.

MATERIAL AND METHOD

Twenty-eight children with acute rheumatic fever, ranging in age from 6 to 11 years, were treated with large doses of corticotropin at the Morrisania City Hospital and were observed from March, 1951, through August, 1953.

There were 20 girls and 8 boys. Seven had at least two previous attacks of rheumatic fever. Fifteen had one attack, and in six there was no definite history. All 28 had mitral insufficiency; in 16 it was associated with mitral stenosis, and 3 also had aortic insufficiency. All except five revealed fluoroscopic evidence of cardiac enlargement involving one or more chambers. Of these five children with normal heart outline, two had both mitral stenosis and insufficiency; the other three showed only mitral insufficiency.

Although 15 of the children were Negroes, none of them had sickle-cell anemia, a condition which is usually associated with cardiac enlargement and is often difficult to differentiate from rheumatic heart disease.[10]

Each patient was observed for one to seven days before the introduction of corticotropin in order to establish beyond question the diagnosis of rheumatic fever and activity. A large number of cases of rheumatic fever were not included in this study either because they were initial attacks or because cardiac damage could not be demonstrated to the examiner's satisfaction.

All the usual procedures for investigation were performed, white blood cell count, eosinophile count (Randolph), erythrocyte sedimentation rate, electrocardiogram, and sodium and potassium blood levels. A daily eosinophile count was done during the course of treatment and three times a week thereafter. The sedimentation test was done three times a week during the hospital stay. Fluoroscopic examination of the heart was performed at least three times a week while in the hospital and at no more than three-month intervals at the cardiac clinic.

Corticotropin was given intramuscularly in a dose of 75 mg. every six hours, four times a day, regardless of age or weight. Most of the children were treated for 14 days, although a few received the medication for 18 days. All children received oral or intramuscular penicillin in doses of 300,000 units per day. None of them was given potassium salts, and blood levels and electrocardiograms revealed that such administration was entirely unnecessary.

The corticotropin was abruptly terminated at the end of the period of treatment, and all children were checked for evidence of rebound phenomena, viz., a rise in the eosinophile count, erythrocyte sedimentation rate, pulse rate, or temperature; pain; redness or swelling of the joints, or precordial or abdominal pain.

The patients remained in the hospital for observation for six to eight weeks. No attempt was made to enforce strict bed rest. In fact, it was practically impossible to keep them in bed, and most of them were ambulatory even during the period of corticotropin treatment. Experience with children treated previously, and not included in the present series, indicated that no untoward effects would result from such leniency.

After the period of hospitalization, the children were either discharged to be followed in the cardiac clinic or were sent to suitable convalescent homes and then returned home for follow-up in the clinic. Each child was checked at intervals of not more than three months, with fluoroscopic study at each visit. Blood cell counts, sedimentation tests, and electrocardiograms were performed regularly. All children received from 100,000 to 200,000 units of oral penicillin daily, as a prophylactic measure.

RESULTS

The Table summarizes the significant features of each of the 28 cases reported. Although the duration of treatment was considerably less than has been recommended by most of the other investigators, there were no appreciable rebound phenomena noted. The only constant condition observed was a sudden sharp rise in the eosinophile count from a level of 0 to counts as high as 1,200 per cubic millimeter, with an average rise between 300 and 400 per cubic millimeter. In several of the children, the pulse rate showed a slight rise, but none demonstrated a tachycardia. The elevation of the pulse rate actually represented a return to a normal level from a relative bradycardia of 70 or less, rather than an elevation from a normal to an increased rate. The persistence of the pulse rate at 80 to 85 per minute suggested that this elevation was not a rebound phenomenon, nor did it indicate a manifestation of the return of rheumatic activity.

There were no cases which showed a rise in temperature above normal. None of the children had an increase in blood pressure, even in those cases with high systolic and pulse pressures from aortic insufficiency.

It was of considerable interest to note that there was no progressive cardiac enlargement during the period of observation. All children had definite evidence of cardiac damage. Twenty-two of them had had previous known attacks of rheumatic fever and had one or more recurrences before admission to the hospital for hormone therapy. The probability that in ordinary circumstances many of the children would have persistent rheumatic activity could not be ignored. Consequently, the absence of changes in cardiac configuration after large-dose treatment suggests that further proliferative changes had been arrested.

It is significant to note that all children were in the preadolescent age period. Experience of many observers over the course of time has repeatedly shown that children with marked cardiac enlargement and even persistent rheumatic activity may undergo a spontaneous regression as they pass through the period of adolescence. Not only may the organic murmurs disappear completely, but there may also be a restoration of the normal cardiac silhouette. This spontaneous return to normal can occur even before adolescence, provided the children remain free of rheumatic activity for an extended length of time. However, in this series of well-established cases of rheumatic fever with one or more recurrences, a tendency toward spontaneous disappearance of abnormal findings is less likely to occur.

Significant Features of the Twenty-Eight Cases Reported

Patient	Age on Adm., Yr.	Sex	Age at Onset of Rheumatic Fever, Yr.	No. Previous Attacks	Cardiac Involvement on Admission		Side Effects of Therapy*	Rebound Phenomena		Period of Observation, Yr.	Changes in Cardiac Findings		Remarks
					Valves	Cardiac Outline		Type†	Severity		Valves	Cardiac Outline	
H. G.	10	M	8	1	MI	Enl. LV	0	1	+	2½	None	Normal size	Complete heart block on adm.
R. C.	10	F	9	1	MI, MS	Enl. LA, LV	0	1	++	2	None	Normal outline	Chorea and rheumatic fever on admission
F. L.	9	F	7	1	MI, MS	Normal	0	1	++	2½	MI	Normal outline	Chorea and subcutaneous nodules on admission
E. F.	10	F	8	2	MI, MS, AI	Enl. RV, LA, LV	0	0	....	2½	None	No change	.....
O. L.	7	M	6	2	MI, MS	Normal	0	1	+	2	None	No change	.....
J. A.	11	M	6	1	MI	Sl. enl. LV	0	1	+	2	None	Normal outline	.....
R. W.	11	F	8	2	MI, MS	Enl. LV	0	0	....	1½	None	Enl. LV	.....
J. M.	9	F	6	1	MI	Enl. PA, LA	0	0	....	1½	None	Sl. enl. LA	.....
L. A.	9	F	5	1	MI	Normal	0	1	+	1½	None	Normal outline	Pericarditis developed during treatment
E. R.	9½	F	7	2	None	Enl. LV	0	0	....	1	None	Normal outline	.....
T. B.	10	F	7	1	MI	Enl. LA, LV	0	1	++	1	None	No change	.....
L. W.	9	F	6	2	MI, MS, AI	Enl. LA, RV, LV	0	1	+++	1	None	No change	.....
A. A.	8	F	Unkn.	..	MI, MS	Enl. LA, LV	0	1	+	8 mo.	MI	Sl. enl. LA, LV	.....
J. D.	6	F	5	1	MI	Normal	0	1	+	1½	None	Normal	.....
G. G.	10	F	7	1	MI	Enl. LA, LV	0	1	++	1	None	Sl. enl. LV	.....
R. H.	7	M	5	1	MI, MS	Enl. LA	0	1	++	1	None	No change	.....
L. H.	10	M	7	1	MI, MS, AI	Enl. LA, RV, LV	0	1	+	1½	None	No change	.....
I. L.	10	F	8	1	MI	Normal	0	1	+	1	No murmur	Normal	.....
L. N.	10	F	7	2	MI, MS	Enl. LA, LV	0	1	++	1½	None	No change	Subcutaneous nodules absorbed in 10 days
E. S.	11½	M	Unkn.	..	MI, MS	Enl. LV	0	0	....	2	MI	No change	.....
J. W.	11	F	Unkn.	..	MI, MS	Enl. LA, LV	0	0	....	1	None	No change	.....
D. W.	10	F	7	1	MI, MS	Enl. LV	1	1	+	2	MI	No change	Chorea
S. H.	9	F	Unkn.	..	MI, MS	Enl. LA, LV	0	1	++	1	MI	No change	.....
C. V.	8	M	6	1	MI, MS	Enl. LA, LV	1	1	+	1	None	No change	.....
M. B.	7	F	Unkn.	..	MI	Enl. LV	1	1	+	2	No murmur	Normal	.....
E. D. N.	9	F	Unkn.	..	MI, MS	Enl. LA, LV	0	1	+	1	None	Normal	.....
I. W.	7	M	6	1	MI	Enl. LV	1	1	+	1	None	Normal	.....
R. C.	6	M	5	1	MI, MS	Enl. LA, RV, LV	1, 2, 3, 4	No effect of corticotropin (ACTH)	....	6 mo.	None	Prog. enl. all chambers	Congestive failure‡

* 1 indicates moon face; 2, glycosuria; 3, hypertension; 4, hirsutism; 5, acne.
† 1 indicates eosinophilia; 2, tachycardia; 3, rise in temperature; 4, change in ECG; 5, rise in E. S. R.; 6, return of joint or abdominal pains.
‡ Transferred to St. Francis' Hospital. Received three more courses of corticotropin and cortisone with no response; died in congestive failure.

An interesting phenomenon was noted on cardiac fluoroscopy shortly after the onset of corticotropin therapy which has not been described previously. Within 24 to 48 hours after the first injection, both right and left ventricles became markedly dilated. The tone of the heart muscle seemed to be appreciably lessened, so that the heart lay on the underlying diaphragmatic surface like a sack of meal. The contractions were not only slowed down but also altered in appearance. They were much less forceful than the previous tumultuous contractions and showed an undulating, almost accordion-like motion. This manifestation, although unusual, was so constant and characteristic that a child with these findings on fluoroscopy could readily be diagnosed as a case under corticotropin therapy. These changes persisted throughout the entire course of treatment, from 14 to 18 days. Within 48 hours after the abrupt cessation of corticotropin, however, they disappeared rapidly, and the ventricular dilatation, "meal-sack" drooping, and accordion-like contractions could no longer be seen. At the present time it is not possible to account for the mechanism responsible for these changes. It may be due to edema of the heart muscle, associated with retention of water and sodium by the corticotropin. None of the children, with one exception who ultimately died, showed evidence of congestive failure, nor were there disturbances of sodium or potassium in the plasma or electrocardiographic changes indicative of hypokalemia. Potassium salts were not administered to the children in this series because studies on previous cases had indicated that hypokalemic effects rarely developed.

COMMENT

The use of doses of corticotropin larger than those recommended and employed by Wilson,[4] Massell,[6] Kuttner,[7] and others was primarily to determine whether the priliferative phase of rheumatic fever could be prevented more effectively and secondarily, whether a short course with large doses could definitely lessen the duration of a bout of rheumatic activity. Bunim,[18] Barnes,[1] and others have maintained that the only effects of hormonal treatment are suppressive and that the disease process, a self-limited one, must inevitably run its course of six to eight weeks unless treatment is continued for the entire duration. Experience with the series reported here would indicate that the use of the larger doses precludes the necessity of prolonged administration of corticotropin. Cessation of therapy was not followed by a flareup of acute manifestations. As Barnes pointed out, it is possible that the doses he employed might have been inadequate.

In order to test further the efficacy of large doses of corticotropin, treatment was abruptly terminated instead of being tapered off gradually. Despite this, rebound phenomena did not occur, with one exception; each child had a rapid rise in the eosinophile count. There was no rise in pulse rate, temperature, or erythrocyte sedimentation rate, and there was no electrocardiographic change. On the basis of these findings, it was concluded that the exudative phase was satisfactorily controlled, and the period of activity could be terminated far short of its anticipated six- to eight-week duration. It must be pointed out here that all children were treated early in the course of active rheumatic infection, so that cessation of activity could not be attributed to a spontaneous regression.

A beneficial effect on the proliferative phase, however, required a more prolonged period of followup. Despite the absence of manifestations of activity, it is conceivable that a low-grade smoldering process could continue for an indefinite

period of time. Taran [12] and Young and Rodstein [14] studied a group of cases with prolonged rheumatic activity. Young and Rodstein set six weeks as the dividing line between the acute and subacute stages. Their results were not particularly gratifying, and they felt that the proliferative phase had not been adequately checked. Taran also stated that the proliferative phase is not necessarily a sequel, but may be a concomitant of the exudative phase. Hence, if the proliferative phase can be quickly and completely controlled, the possibility of prevention of scarring could be proportionately enhanced. Bunim [13] has shown that it is possible for rheumatic activity to exist when all tests for activity are negative. He found Aschoff nodules in auricular appendages removed in the course of mitral commissurotomy. Since the usual tests for activity may often be absent, some other criterion must be employed to indicate persistence of the disease process. It was believed that the ultimate criterion of activity is progressive cardiac enlargement.

This aspect was studied by repeated fluoroscopic examinations of the hearts of these children during a period of observation ranging from 12 to 30 months. None of the children showed evidence of progressive enlargement, and several actually had a diminution. This latter feature could not always be due directly to the method of treatment, since all children were admitted with active rheumatic fever, and many already had cardiac dilatation, which could subside with the conclusion of activity. Although the length of time of observation may be considered as inadequate in dealing with a disease of such a protracted nature, it must be stressed that all these children had one or more recurrences of rheumatic fever, all had definite valvular and/or myocardial damage, and all were active on admission. The potentiality for progressive cardiac enlargement in these children in such a selected series should, therefore, be expectedly high.

Corticotropin was not expected to prevent exacerbations of rheumatic fever. The fact that these did not occur in any of the children could with greater justice be attributed to the prophylactic penicillin than to the hormonal therapy. All patients received oral penicillin while attending the cardiac clinic or during their stay at convalescent homes. It must be understood that penicillin should not have any effect on a smoldering rheumatic infection. Aside from the possibility of spontaneous subsidence, the prevention of such low-grade activity could be ascribed only to the effect of corticotropin.

A high percentage of children treated by other investigators with corticotropin and/or cortisone have developed certain undesirable side-effects. It was interesting to note the minimal number in this series, despite the large doses used. None of the children developed hypertension, hyperglycemia, or hirsutism, with the sole exception of the one ultimately fatal case. A few showed a moon face, and three of the children became distended.

The relative freedom from these manifestations of the Cushing-syndrome effect is attributed to two factors: first, the short period of treatment in comparison to the usual prolonged procedure, and second, the absence of congestive failure and liver dysfunction in all cases but one. This one child failed to show a satisfactory response to three full courses of treatment and with each course demonstrated all the undesirable side-effects mentioned, including striae, acne, and hirsutism. He was in congestive failure on admission, showed no improvement at any time, and became worse with each course. Whereas most of the other children became euphoric under treatment, he was profoundly depressed. We considered it significant that he

alone of all the children was not only jaundiced but also had impairment of liver function. Laboratory tests revealed extensive hepatic injury. It was believed that his failure to respond in the same fashion as all the other children was in some way related to this disturbed liver function, and similar instances of unsatisfactory responses in other series of cases may conceivably be due to the same cause.[15]

One of the children developed pericarditis at the onset of treatment, a circumstance noted by Dorfman [8] and McCrory and Friedman.[16] However, her subsequent course was as satisfactory as all the others, with good results.

SUMMARY

Twenty-eight children with definite evidence of rheumatic heart disease who were admitted to the hospital with an acute exacerbation of rheumatic fever were treated with 300 mg. per day of corticotropin, intramuscularly, for a period of 14 to 18 days.

On the abrupt cessation of therapy, no significant rebound phenomena or flareup of rheumatic activity took place.

A minimal number of mild side-effects occurred.

Certain characteristic changes in the cardiac silhouette developed during the course of treatment.

A follow-up period of 12 to 30 months revealed no increase in the size of the various heart chambers, suggesting that progressive rheumatic activity had been checked or prevented.

One case who failed to respond to three courses of corticotropin is included in this series. Failure to respond to treatment as all the others did has been ascribed to complicating severe liver damage.

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PULMONARY HYALINE MEMBRANES IN INFANTS OF DIABETIC MOTHERS

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THAT NEWBORN infants of diabetic mothers have a high neonatal mortality has long been known.* Postmortem examinations of such infants have shed little light on the exact nature of the factors responsible for death. The most extensive review of this problem has been made by Warren and LeCompte,[3] who analyzed the postmortem findings of 50 infants of diabetic mothers and concluded that the cause of death in the majority of the infants of their series was not clear. They noted, however, certain characteristic findings, namely, macrosomia, visceromegaly, and hyperplasia of the islets of Langerhans, together with infiltration of eosinophilic leukocytes.

Miller † has been particularly impressed by the cardiac enlargement of infants of diabetic mothers and has attributed the high neonatal mortality rate to cardiac failure. He based his conclusions not only on the weight of the heart at autopsy, but on the size of the heart by x-ray. The latter is notoriously a poor technique for judging heart size in the newborn, and the former cannot be used to determine the presence or absence of cardiac failure.

We ‡ have been particularly impressed by the respiratory difficulty encountered in newborn infants of diabetic mothers and have noted no clinical findings compatible with a diagnosis of cardiac failure. It has been our contention [9] that the characteristic clinical picture exhibited by infants of diabetic mothers is due not to cardiac failure, but to pulmonary hyaline membranes, and that the respiratory distress is similar to that seen in the post-Caesarean-section syndrome.

The infant of a diabetic mother may show no abnormal signs and may have a completely normal course, or may exhibit respiratory distress immediately after birth. Frequently, the signs of respiratory distress may be present, but minimal, at birth and become striking in their manifestations within a few hours following delivery. The signs consist of increased respiratory rate, with or without cyanosis, together with retractions of the soft tissues of the chest wall and a constant complaining cry. Examination reveals poor aeration of the lungs and inspiratory rales, which are inconstant but heard throughout the lung fields. X-ray reveals a fine

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* References 1 and 2.

† References 4-6.

‡ References 7 and 8.

diffuse type of atelectasis throughout the lungs. The respiratory distress becomes increasingly severe over the next hours of life, and the infant dies of respiratory failure after 24 to 72 hours or very gradually begins to improve and recovers completely over the same period of time.

In order to evaluate the role of pulmonary hyaline membranes as a cause of death in infants of diabetic mothers, a series of infants born of diabetic mothers and dying between the ages of 1 hour and 14 days has been studied to determine (1) the presence of a significant anatomical cause of death, (2) the presence of hyaline membranes in the lungs, and (3) the relation of the hyaline membranes to Caesarean section in such infants.

MATERIALS AND METHODS

The microscopic sections of the lungs of all infants born of diabetic mothers and dying between the ages of 1 hour and 14 days who were examined at autopsy at the Faulkner Hospital and the Children's Hospital from 1935 to 1951 were studied and the protocols were reviewed. These age limits were set because at least one hour of breathing has previously been found to be necessary for the production of pulmonary membranes. The slides were routine sections stained with hematoxylin and eosin or with eosin-methylene blue; more than one section of the lung was available in 32 of the 40 cases studied. Measurements of the weight at death were available in 36 cases and crown-heel length in 36 cases; in the single case in which both these measurements were absent there was other evidence to indicate the approximate degree of maturity. The protocols were studied to determine the presence of a reasonable cause of death, with objective pathological changes other than the presence of atelectasis or pulmonary hyaline membranes. The slides were rated as to the degree of atelectasis, the presence of squamous cells, and the extent of hyaline membrane formation. The latter change was classed as significant if one-half or more of the aerated terminal bronchioles, alveolar ducts, and alveoli were lined with hyaline membranes.

The number of sections available and the degree of correlation of the pathological changes within a given section and among the various sections in each case were also noted. With the degree of membrane formation rated on a basis of 0 to 4+, a set of slides was considered to lack correlation if the average of the differences between the pairs of slides exceeded one degree.

Heart weights were tabulated and compared with the expected weight based on the averages of Potter and Adair.[10] Since the body weights of the infants studied frequently exceeded that predicted in the above averages for the crown-heel length, expected heart weights were arrived at by interpolation. Any heart weighing more than 25% above the expected weight was classed as overweight.

RESULTS

The 40 infants studied were divided into two groups, those having a major anatomical cause of death regardless of the presence or absence of hyaline membrane formation and/or atelectasis and those having no other type of explanation of death. Each group was further subdivided as to the presence or absence of significant hyaline membrane formation. The results are listed in Table 1. Thirteen, or less than one-third, had what was considered a major cause of death; tentorial tear and/or subarachnoid hemorrhage, six cases; hemolytic disease with kernicterus, two cases; severe pneumonia, two cases, and cor triloculare biventriculare, pneumothorax, and encephalocele with hydrocephalus, one case each. Only three of these 13 also had hyaline membrane formation. Of the remaining 27 cases, 21, or more than three-fourths, had a significant hyaline membrane formation.

Correlation of the findings of the slides of a given case was usually good; of the 32 cases in which 2 or more slides were available, 5 showed lack of correlation,

although in the 9 cases in which 4 or more slides were available, 3 failed to correlate. Two of these latter cases, however, had sufficient membrane formation so that they were classed as significant.

In the 37 cases in which the method of delivery was given, there were 22 instances of Caesarean section. Sixty-eight per cent of the infants delivered by Caesarean section showed the development of significant amounts of hyaline membranes, whereas 53% of the infants delivered from below showed this abnormality (Table 2).

TABLE 1.—*Cause of Death, with Relation to Presence of Membranes*

	With Membranes	%	Without Membranes	Total	%
Major cause of death	8	23	10	18	32
No major cause of death	21	78	6	27	68
Total	24	60	16	40	100

TABLE 2.—*Relation of Membranes to Method of Delivery*

	With Hyaline Membranes	Without Hyaline Membranes	% With Hyaline Membranes
Diabetic			
Caesarean section	15	7	68
Pelvic delivery	8	7	53
Controls [11]			
Caesarean section	28	12	70
Pelvic delivery	97	139	41

TABLE 3.—*Relation of Membranes to Heart Weight*

	With Hyaline Membrane Disease	Without Hyaline Membrane Disease
Normal weight	14	6
Overweight	10	9
% with enlargement	42	60

Table 3 shows the relationship between heart weight and hyaline membrane formation in the 39 cases in which this measurement was available. Forty-two per cent of those with membranes showed significant enlargement of the heart, as opposed to 60% in those without hyaline membrane formation.

COMMENT

The incidence of pulmonary hyaline membranes in infants born of diabetic mothers is definitely greater than in infants at large dying in the first few days of life. In the cases studied, 63% dying between the ages of 1 hour and 72 hours had membranes, as compared with 37% in the general series presented by Blystad, Landing, and Smith.[11] Miller and Jennison,§ in their series of 71 autopsies on

§ References 12 and 13.

infants dying in the neonatal period (classed as dying after birth and before 9 to 10 days in full-term infants and before 30 days in prematures), cite 19 examples (27%) of "hyaline-like material" among "significant causes" of death and 28 examples altogether (39%), regardless of the cause of death.

The comparison as regards clear-cut causes of death is less readily obtained. In this series of infants of diabetic mothers, pulmonary hyaline membranes were present in only 23% of the infants having some other clear-cut cause of death, but in 78% of the remaining infants. Similar analysis of the data on the 56 cases of neonatal death presented by Miller gives about the same figure (24%) in the presence of another adequate cause of death (31 cases), but showed hyaline material in significant amount (3 to 4+) in only 52% of the remaining cases. Unfortunately, the large series of Blystad and co-workers[11] is not broken down in terms of pathologic diagnosis in the infant. It would appear, nevertheless, that pulmonary hyaline membranes are definitely more common as a cause of death in infants of diabetic mothers, if this lesion can indeed be assumed to be lethal.

The significance of hyaline membranes as a cause of death remains to be positively determined. In this material, it was usual to see atelectasis of at least three-fourths of the alveoli, with a major portion of the remaining aerated spaces lined by a layer of hyaline material 10 to 20 μ in thickness (as estimated by comparison with erythrocyte diameters); moreover, these aerated spaces are very often dilated terminal bronchioles and alveolar ducts, rather than alveoli. It is difficult to believe, on morphological grounds alone, that this material can be anything less than a physical impediment both to the diffusion of oxygen into the capillaries and to the distal penetration of air into the alveoli. The recent work of Behrle and his co-workers[14] gives positive evidence in support of the latter point. The objection may be raised that in most cases very few sections of the lungs were available for examination, that the sections were probably taken from those portions of the lungs which appeared most abnormal on gross examination, and, thus, that the material examined may very well not be representative of the total pulmonary picture. The lack of correlation in three of the nine cases having four or more slides available bears out this contention. However, it is the frequent observation that infants presenting this pathologic picture have been noted to have labored respirations, retraction of the rib cage, cyanosis, and diminished breath sounds as the principal clinical findings. This theory is entirely compatible with the theory of obstruction by hyaline membranes, but correlation of the clinical picture with the findings in multiple sections, both from dependent and from superior portions of the lungs of a large series of early neonatal deaths, would be necessary in order to test this point critically. No such analysis has yet been reported.

Regardless of the significance of the hyaline membranes as a cause of death, it is interesting to note the correlation of the occurrence of the membranes with the mode of delivery. In the large series of Blystad and co-workers,[11] hyaline membranes were found in 70% of the infants dying after Caesarean section, as compared with 41% after pelvic delivery. In the present series of infants of diabetic mothers, the incidence was 68% and 53%, respectively. The relation is apparent in the work of Gellis, White, and Pfeffer,[8] who pointed out the increased amount of amniotic fluid present in the stomachs of infants delivered by Caesarean section as compared with pelvic deliveries, and in the studies of Blystad and co-workers,[11] who feel that the pulmonary hyaline membrane in the newborn infant has its origin in the aspiration

of amniotic fluid. Maternal diabetes must in some manner, as yet to be determined, set the stage in the infant for the development of pulmonary hyaline membranes. There appears to be little doubt that Caesarean-section delivery increases the risk of pulmonary hyaline membranes not only in the infant of a diabetic mother, but in any infant. The choice of Caesarean-section delivery in infants of diabetic mothers thus appears to be unwise; however, the high fetal death rate in such infants justifies the increased risk of pulmonary hyaline membranes from Caesarean-section delivery.

It has been suggested by Miller || that the death of many infants of diabetic mothers was related to congestive cardiac failure, based on the finding of an enlarged cardiac silhouette by x-ray examination. It has been further suggested [15] that the mechanism of congestive failure has a bearing on the development of the pulmonary membrane. In this series of infants, there is a complete lack of correlation between the presence of cardiomegaly and the presence of membranes. Furthermore, the study of the clinical findings in a consecutive series of nearly 600 infants born of diabetic mothers ¶ showed in the distressed persons, dying or surviving, a uniform picture of cyanosis, retraction, rapid respirations, and diminished breath sounds indicative of peripheral respiratory obstruction. In no case, in the absence of a congenital malformation of the heart, was there the enlarging liver, edema, and venous distension on which a diagnosis of congestive failure could be made. Since the heart silhouette size by x-ray or heart weight at autopsy is, in the absence of associated clinical findings, insufficient for the diagnosis of congestive failure, it is unlikely that the death of these infants and/or the appearance of hyaline membranes can be related to congestive failure.

SUMMARY AND CONCLUSIONS

Microscopic sections of the lungs of 40 infants born of diabetic mothers and dying in the neonatal period have been studied for the presence of hyaline membranes.

Hyaline membranes were found in the lungs of three-fourths of the infants lacking some other major cause of death, but in only one-third of those with a major cause of death.

The election of Caesarean section was felt to be significant in increasing the incidence of pulmonary hyaline membranes in infants of diabetic mothers but appears justified in view of the high fetal mortality.

Pulmonary hyaline membranes were felt to occur in the absence of and without relation to congestive heart failure.

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GROWTH AND METABOLISM IN NORMAL AND THYROID-ABLATED INFANT RHESUS MONKEYS (MACACA MULATTA)

VII. Morphology of Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta)—Skeletal System

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INTRODUCTION

MORPHOLOGIC observations pertaining to the skeletal systems of normal and athyroid infant macaque monkeys are presented in the present communication, and certain correlations are made with preceding clinical, biochemical, and radiological observations on growth and metabolism in those animals.*

Investigation of skeletal development in human cretinism is limited by multiple intrinsic and extrinsic factors which cannot be controlled. Experimental observations based on subprimates cannot always be applied to humans; therefore, it is logical to use a catarrhine laboratory animal in such studies. With selection of the primate Macaca mulatta for study, many intrinsic and extrinsic factors are subject to control.[1]

The present study has been confined to early infancy, when growth and development is not only rapid but strikingly constant among normal colony members.† Control of extrinsic factors was facilitated by animal quarters which provided constant temperature, humidity, and physical environment. In addition, disease and nutritional deficiencies were maintained at a minimum by standardization of an optimal dietary regimen, with vitamin and iron supplements.[1]

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* References 1-6.

† References 1, 4, and 5.

METHODS

In one group of animals, thyroid ablation had been accomplished by the administration of approximately 2 mc. of radioactive iodine (I^{131}) during early infancy.[2] Athyrosis was based upon (*a*) failure of the animals to concentrate tracer doses of I^{131} in the anatomical thyroid area ‡; (*b*) a marked and sustained fall in serum-precipitable iodine from normal (4 to 8 γ per 100 cc.) to below 1 γ per 100 cc.[6]; (*c*) a pronounced slowing of linear bone growth and retardation of skeletal maturation,[5] and (*d*) development of physical features generally described in human cretins, such as thick myxedematous skin, coarse dull hair, protuberant abdomen, umbilical hernia, macroglossia, and delayed eruption of deciduous teeth.[2] All thyroid-ablated animals were also studied for evidence of hypoparathyroidism.[2]

Four animals were killed at approximately 270 days of age for morphological study. Two animals, C-794 and M-782, were normal controls. Two animals, S-775 and P-790, were athyroid, having undergone I^{131} ablation in early infancy. Animal S-775 was selected as representative of the four athyroid infants extensively studied with respect to altered metabolism and retarded growth over a period of 150 days.§ Animal P-790 was selected from a second group of four athyroid infants in which the effects of replacement therapy with crystalline *l*-thyroxine had been evaluated over a 90- to 120-day period. During that study, the general metabolic and skeletal responses to varying doses of *l*-thyroxine were observed.[3] During low levels of thyroxine therapy (6 γ per kilogram of body weight per day), most general metabolic processes returned to normal, while skeletal retardation persisted to a degree comparable to that in untreated athyroid animals. It was found necessary to increase the thyroxine dosage to higher levels (20 γ per kilogram of body weight per day) before the skeletal systems of the athyroid animals manifested a normal response. Thus, a differential response between general metabolic processes and bone development occurred during therapy. During that phase of study, Animal P-790, previously athyroid for 120 days, was maintained on the inadequate dose of 6 γ per kilogram per day of thyroxine for 90 days and killed 30 days thereafter.

In addition, tissues from two other normal animals (Y-581 and Y-623) of comparable age were incorporated into the histology of the control group.

OBSERVATIONS

Only that morphology pertaining to the skeletal systems of normal and athyroid infant monkeys is reported in detail. Included, however, is a limited presentation of certain endocrine glands, mainly to substantiate the completeness of thyroid ablation and the integrity of the parathyroid glands.

Endocrine.—Thyroid glands of the normal animals were situated at the level of the second to fourth tracheal cartilage. They were of the usual size and structure, with weights ranging from 150 to 190 mg. Follicles varied somewhat in size, yet colloid storage and cuboid lining epithelium were uniform (Fig. 1*A*).

In the I^{131}-treated animals it was grossly impossible to identify either thyroid or scar tissue within the neck. Microscopic foci were identified as the only remnants of the thyroid gland in serial sections of laryngotracheal tissue. These were fusiform and ranged from 0.4 to 0.6 mm. in length. Glandular residua consisted of predominantly dense collagenous fibrous tissue (Fig. 1*B*). Within this relatively avascular stroma were a few small nests of thyroid epithelium. Individual cells were distorted, small, and pyknotic. Thyroid follicles were absent, although small globules of refractile eosinophilic material were occasionally observed. These resembled inspissated colloid, yet were not usually associated with epithelial cells. In addition, there was focal hemosiderin deposition and moderate vascular sclerosis.

‡ References 2 and 6.

§ References 2, 5, and 6.

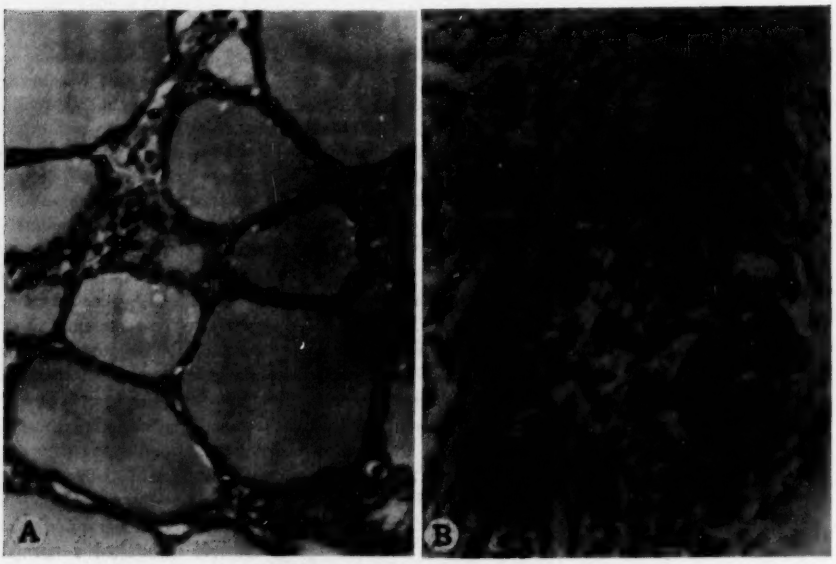

Fig. 1.—Thyroid tissue. *A*, normal—although follicles vary in size, colloid is homogeneous, and lining cells are uniformly flat or cuboidal. *B*, I^{131}-ablated—in this complete cross section of the thyroid remnant, only one minute follicle can be identified (below). A few nests of distorted pyknotic thyroid epithelial cells persist in the dense collagenous tissue.

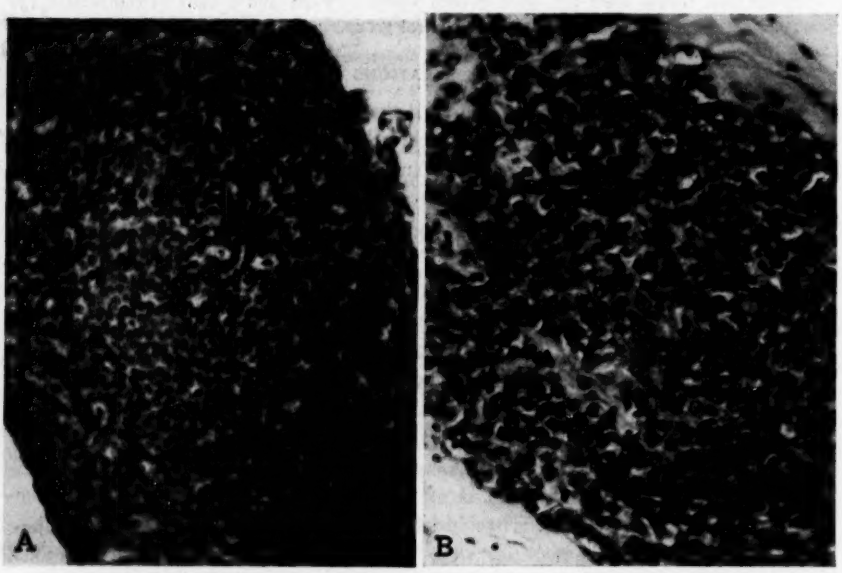

Fig. 2.—Parathyroid gland. *A*, normal—small uniform closely spaced principal cells predominate and exhibit a cord-like arrangement about capillaries. *B*, athyroid—glandular epithelium is disorderly in arrangement. Marked cellular pleomorphism is associated with increased amounts of both vacuolated and granular cytoplasm and variation in nuclear chromatin.

In the normal animals, the parathyroid glands were either closely applied to the posterior thyroid capsule or, less commonly, incorporated within thyroid parenchyma. The glands ranged between 0.7 and 1.0 mm. and were comprised exclusively of small uniform principle cells (Fig. 2*A*). In the I^{131} thyroid-ablated animals, parathyroid glands were approximately two-thirds the size of the normals and were usually delicately encapsulated. However, when they were closely associated with the scarred thyroid remnant, there was moderate capsular fibrosis. In such incidences, intrinsic stroma and vascularity remained unaltered. Principal cells were less orderly in arrangement and larger than those of the normal (Fig. 2*B*). These larger cells were moderately pleomorphic, with increased cytoplasmic vacuolization and variation in nuclear chromatin. Numbers of large "oxyphile" cells with prominent cytoplasmic granules were also observed.

Pituitary glands in normal animals were of usual structure and weighed approximately 30 mg. The adenohypophysis was composed of epithelial cells arranged in loose aggregates and supported by delicate reticular connective tissue (Fig. 3*A*). There was the usual proportion of chromophobe, alpha, and beta type cells. In the thyroid-ablated animals, the pituitary glands were approximately two times normal size and had produced symmetrical enlargement of the sella turcica and thinning of the anterior clinoids. Hyperplasia and hypertrophy of beta cells throughout the anterior lobe accounted for the pituitary enlargement (Fig. 3*B*). These cells were evenly distributed, closely spaced, and ranged up to four times the normal size. Cytoplasm was abundant, exhibiting the characteristic "hyalinization" and vacuolization. Chromophobe and alpha type cells were inconspicuous.

Skeleton.—In thyroid-ablated infant animals there was a generalized retardation in skeletal development. This was manifested as a linear and circumferential growth deficit, a delay in skeletal aging, and an alteration in bony reorganization. Skeletons of these animals were short, relatively broad, and dense. There was a persistence of infantile characteristics. A few minor, but apparently specific, deformities developed.[5]

Ossification was retarded in both cartilagenous and membranous bone. Delay in periosteal ossification, although not as marked, was nevertheless evident. The various phases of bone development and the types of ossification were best illustrated in the tibiae, the vertebrae, and the cranial bones.

Dwarfing, a deficiency essentially of linear bone growth, was reflected not only by the shortness of tubular bones but also in the small size of flat bones and in the decreased volumes of the cranial vault, thoracic cage, and pelvis. Athyroid animals exhibited a linear deficit of 2 cm. in the tibia alone.[5]

In the athyroid animals, growth deficiency of long bones was characterized primarily by the retardation of endochondral ossification. In the normal animals, epiphyseal endochondral ossification was active. The epiphyseal cartilage of the proximal tibia was approximately 1 mm. in width. There was an equal division between unorganized hyaline cartilage and columnar hypertrophic cartilage (Fig. 4*A*). Toward the zone of provisional calcification, columns with increasing cellular hypertrophy, vesiculation, and flattening broadened into truncated cones (Fig. 5*A*). In the zone of vascular erosion, such cones frequently coalesced, leaving little intervening calcified cartilage matrix. Numbers of vascular buds penetrated into the cones of hypertrophic cells (Fig. 6*A*). Intervening bars of cartilagenous matrix were

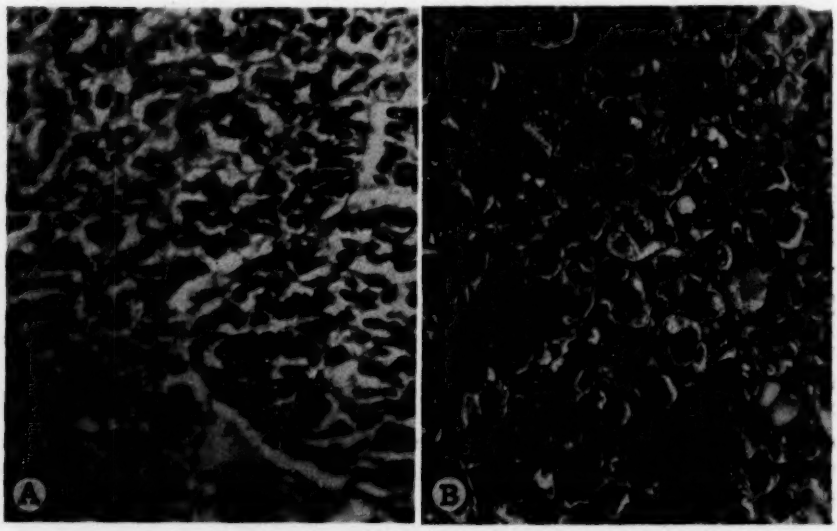

Fig. 3.—Adenohypophysis. *A*, normal—loose aggregates of epithelial cells are delicately supported, and chromophobe-type cells predominate. *B*, athyroid—marked hypertrophy and hyperplasia of beta cells obscure other cell types. Note characteristic hyalinization and vacuolization of cytoplasm of the beta cells.

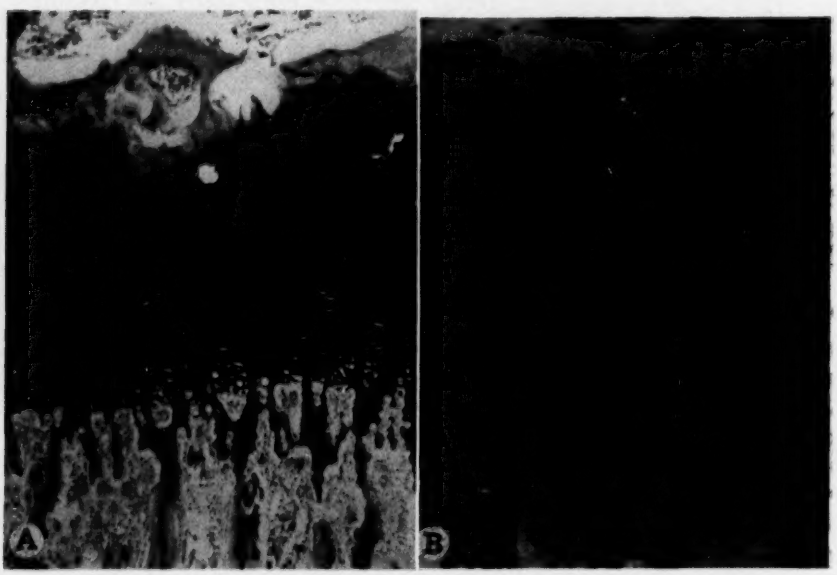

Fig. 4.—Epiphyseal line; proximal tibia. *A*, normal—approximately one-half of the narrow epiphyseal cartilage is of the columnar type. Overlying epiphyseal bony plate is well formed. *B*, athyroid—compared with the normal, the epiphyseal cartilage is broader, a result particularly of increased unorganized cartilage. Note relative abundance of matrix.

surrounded by numbers of osteoblasts. Osteoid was deposited, and, as it calcified, primary bone trabeculae were formed about the cartilage bars (Fig. 7*A*). As these trabeculae underwent continued ossification, cartilagenous matrix became inconspicuous.

In the athyroid animals, epiphyseal lines were always broader, ranging up to 30% above the normal. This was associated with an increase in unorganized hyaline cartilage and, to a lesser degree, columnar cartilage (Fig. 4*B*). In both zones there was a relative abundance of cartilagenous matrix. Columns of cartilage were not only longer but were also narrower and straighter (Fig. 5*B*). Toward the zone of provisional calcification, such columns showed less tendency to broaden into cones. This was correlated with a decrease in size, vesiculization, and flattening of the

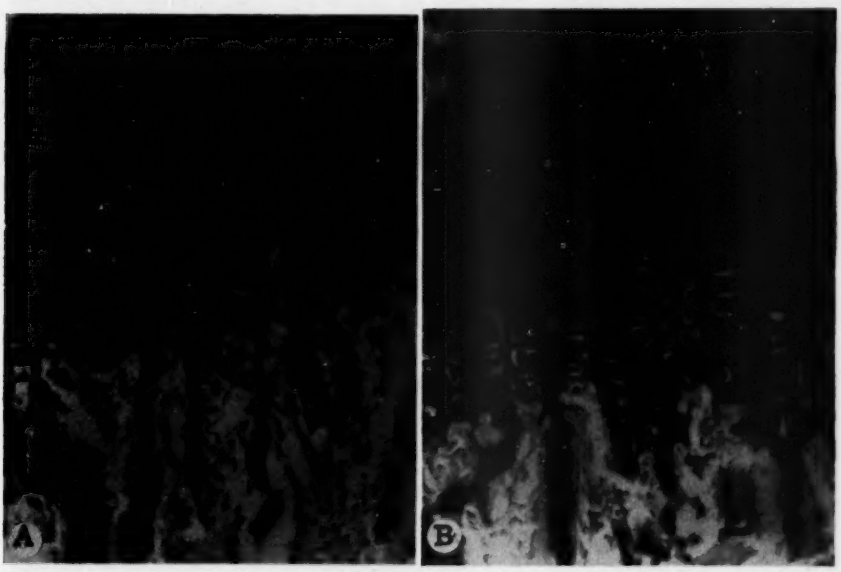

Fig. 5.—Columnar cartilage—epiphyseal line, proximal tibia. *A*, normal—cells of the cartilagenous columns are undergoing hypertrophy, vesiculation, and flattening. Note tendency for these columns to broaden and coalesce at the zone of erosion (midleft). *B*, athyroid—compared with the normal, cells of the cartilagenous columns exhibit less vesiculation and flattening. These narrower and straighter columns with more intervening matrix show less tendency to coalesce.

hypertrophic cells. Thus, there was a delayed transformation or maturation of columnar cells into hypertrophic cells. The narrow columnar alignment of these cells, coupled with the greater abundance of matrix, resulted in less coalescence of hypertrophic columns at the zone of erosion. Fewer buds of vascular connective tissue penetrated into the zone of erosion, their number and distribution corresponding to the available hypertrophic cartilage (Fig. 6*B*). These buds were narrower, as if confined by the broader intervening trabeculae of cartilagenous matrix. There was a definite paucity of fibroblasts, osteoblasts, and osteoclasts in this zone. Despite this, deposition of osteoid upon primary trabeculae and subsequent calcification appeared to be unaltered. Incompletely eroded cartilage was incorporated into the

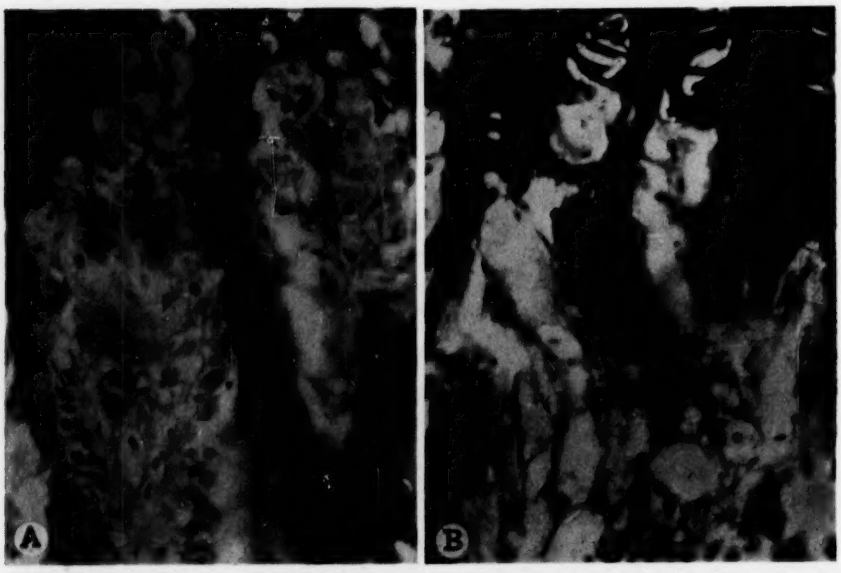

Fig. 6.—Cartilagenous erosion—epiphyseal line, proximal tibia. *A*, normal—buds of vascular richly cellular connective tissue penetrate vesicular cartilage from below. Note density of osteoblasts, deposition of osteoid, and formation of osteocytes (lower right). *B*, athyroid—compare the decreased vascularity and osteoblastic cellularity with the normal. Note presence of fat cells (below).

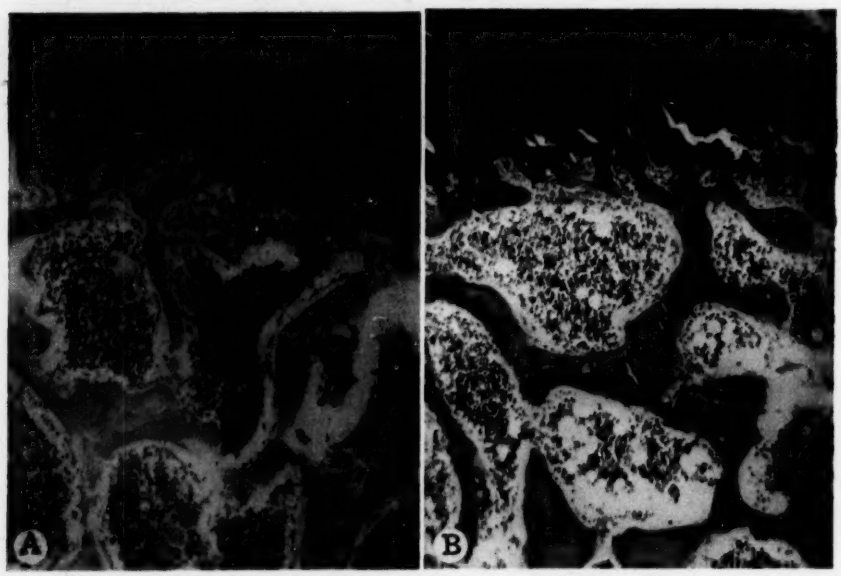

Fig. 7.—Primary bone trabeculae—vertebra. *A*, normal—as primary bone trabeculae form below the epiphyseal cartilage, continued ossification is associated with almost complete utilization of cartilage. *B*, athyroid—compare the coarser primary bone trabeculae with the normal. Note that islets of epiphyseal cartilage persist within these trabeculae.

primary bone trabeculae to a much greater extent than in the normal and contributed to the initial thickness of these structures (Fig. 7*B*). These islets resisted ossification and were conspicuous deep in the diaphyseal shaft.

Thus, in the athyroid animals, endochondral ossification was altered at the epiphyseal line by (*a*) an increase in cartilage, particularly matrix; (*b*) delayed maturation of columnar cells into hypertrophic vesicular cells; (*c*) decreased vascularity and cellularity at the zone of erosion, and (*d*) incomplete erosion or ossification of cartilage.

Fibrous suture lines united cranial membranous bones of both the normal and the athyroid animals. In the normal animals, these synosteal unions were narrow, with sharp straight fibro-osseous junctions (Fig. 8*A*). Ossification was moderately active, as indicated by the cellularity, vascularity, and transformation of fibrous cells into osteoblasts and osteocytes.

In the athyroid animals, synosteal unions were abnormally broad, with irregular serrated fibro-osseous junctions (Fig. 8*B*). As compared with the normal, suture lines were often three times as broad. Synosteal zones were relatively fibrous and acellular, exhibiting a predominance of dense collagenous stroma, a paucity of proliferating fibroblasts, and a decreased vascularity. There was diminished transformation of the fibrous cells into osteoblasts and osteocytes. Here, relatively inactive fibrous tissue abutted directly against dense cancellous bone.

Periosteal ossification in the normal animals was moderately active, as indicated by the number of osteoblasts between the delicate periosteum and cortical bone surface (Fig. 9*A*). In the athyroid animals, there was less retardation of periosteal ossification than of endochondral ossification, a circumstance contributing to the relative thickness of bones; external diameters were only slightly less than those of the normals. Despite this fact, there was a definite decrease in the number of osteoblasts, and the periosteum was more fibrous and less vascular (Fig. 9*B*).

In normal animals, as spongy bone was resorbed and new bone formed, medullary cavities enlarged, and cortices became thinner and more compact. In this phase of skeletal reconstruction, bony resorption was related to osteoblastic activity and vascularity, as judged by the number and prominence of these elements (Fig. 10*A*).

Bony reconstruction was markedly retarded in the athyroid animals, particularly that phase relating to bone resorption. Thus, medullary cavities were smaller than normal, and spongy bone tended to persist as coarse trabeculae throughout the shaft. Cortices were relatively thick, since internal resorption lagged behind periosteal deposition. These features contributed to the increased density of bone. Bone density consistently increased in athyroid animals and was determined to be approximately 1.6 times that of the normal.[5] Except for a decreased ratio of osteocytes to bony matrix, cortical Haversian systems were not unusual. Haversian canals were smaller and more tubular, particularly towards the inner cortex (Fig. 10*B*). Canular extensions of the medullary spaces into the adjacent cortical bone were fewer and less intricate. Spongy bone trabeculae throughout the shaft were broader and more irregular, a feature accentuated in endochondral bone by the incorporated islets of unresorbed cartilage.

There was an associated alteration in osteoblastic activity throughout the cortex and medulla, as indicated by the number, alignment, and size of these cells. In the normal animal, closely spaced polygonal osteoblasts consistently bordered the bone margins of the Haversian canals and trabeculae (Fig. 11*A*). In the athyroid animal

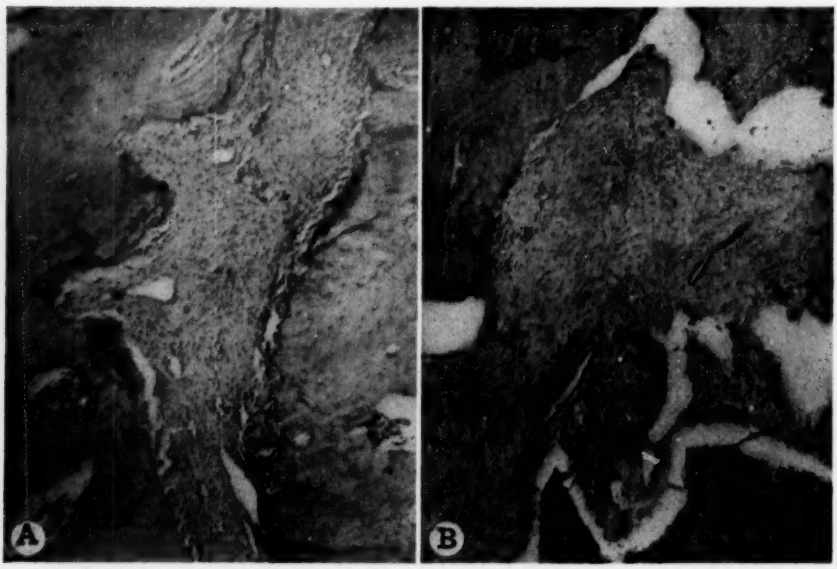

Fig. 8.—Cranial interparietal suture line. *A*, normal—along the margins of relatively straight fibrous unions are narrow zones of osteogenesis. *B*, athyroid—compared with the normal, fibrous unions are broader and more irregular. Collagenous stroma is prominent and associated with decreased cellularity, vascularity, and osteogenesis.

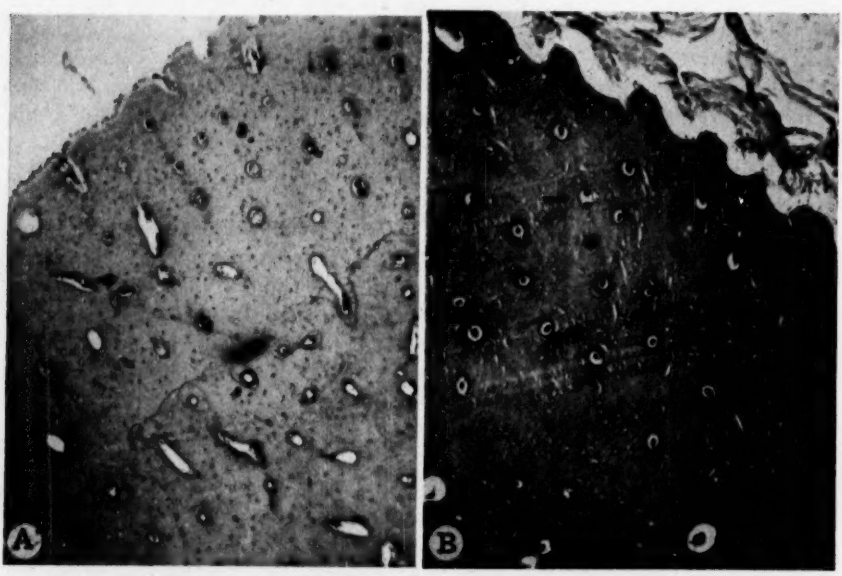

Fig. 9.—Periosteum and outer cortex—midtibia. *A*, normal—numbers of osteoblasts line the cortical bone surface. *B*, athyroid—periosteal osteoblasts are less numerous. Note dense fibrous periosteum.

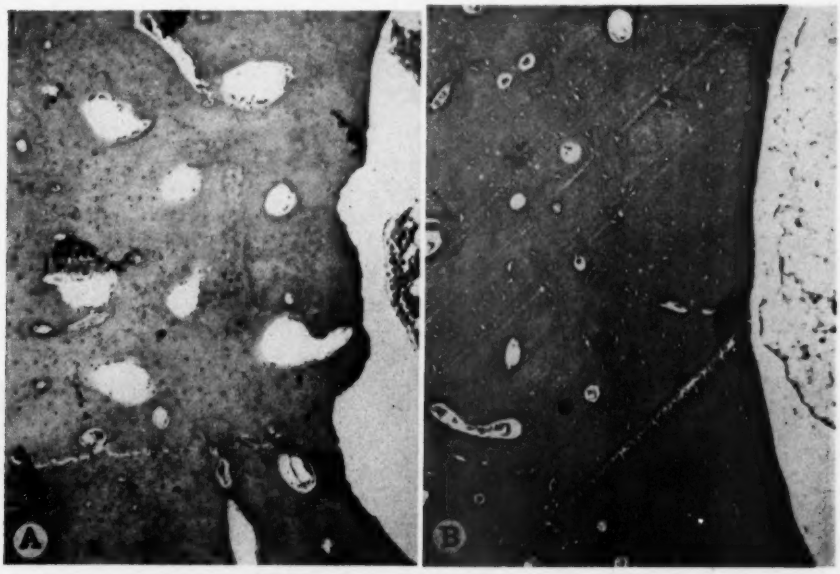

Fig. 10.—Inner cortex and endosteum—midtibia. *A*, normal—prominent Haversian canals are well vascularized and bordered by numbers of osteoblasts. *B*, athyroid—Haversian canals are smaller and more tubular, as compared with normal, and lining osteoblasts are less numerous. Note the decreased ratio of osteocytes to bone matrix and the straighter corticomedullary junction.

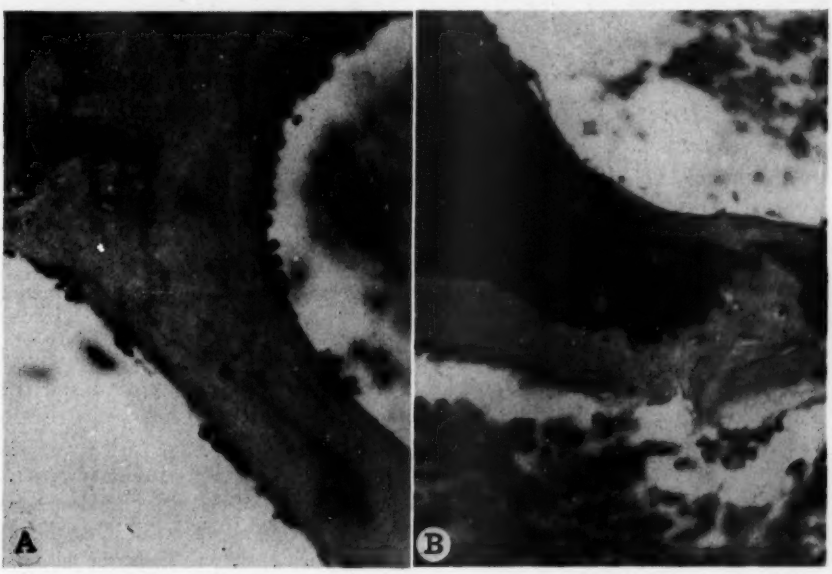

Fig. 11.—Medullary trabeculae—proximal tibia. *A*, normal—closely spaced polygonal osteoblasts line the trabecula. *B*, athyroid—as compared with the normal, osteoblasts lining the trabecula are sparse, small, and fusiform. Note persistence of cartilagenous matrix within the bone trabecula.

osteoblasts at these sites were relatively sparse, small, and fusiform (Fig. 11*B*). They were closely applied to the adjacent bone matrix in a manner which, at times, rendered their identification difficult.

Thus, in the athyroid animals, altered skeletal reconstruction was primarily related to a retardation in bone resorption. This retardation resulted in bones of increased density, with thick cortices, small medullary cavities, and an abundance of trabeculae. There was an associated decrease in the size of Haversian canals, in the ratio of osteocytes to bone matrix, and in both osteoblastic cellularity and vascularity.

At the time of death, medullary hematopoiesis of normal animals was active. In the axial, tubular, and flat bone, medullary spaces were well filled with hematopoietic cells (Fig. 12*A*). In the more peripheral appendicular bones, hematopoietic

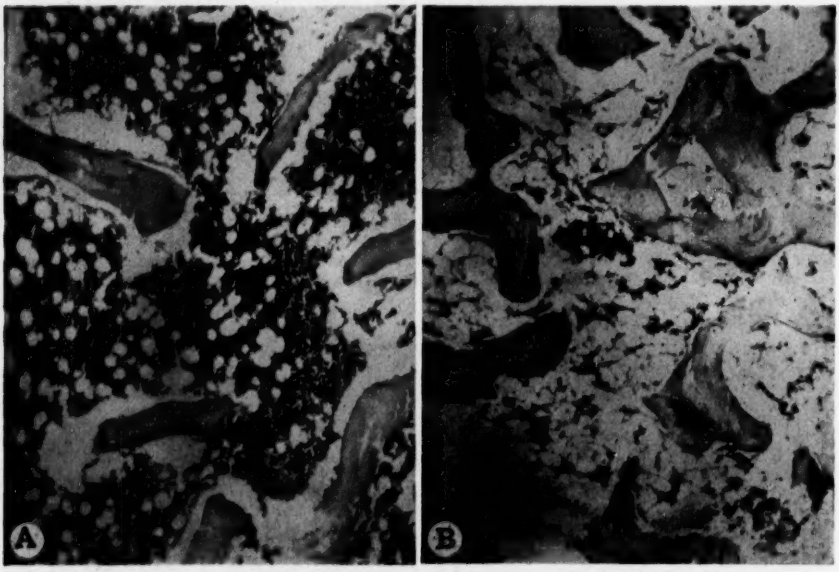

Fig. 12.—Medullary space—vertebra. *A*, normal—medullary spaces are well filled with blood-forming cells, indicating active hematopoiesis. *B*, athyroid—as compared with normal, medullary spaces are predominantly fatty, with hematopoietic centers small and well spaced. Note the prominence of bone trabeculae.

cells were admixed with increasing numbers of fat cells. For example, the medullary space of the midtibia was equally divided between hematopoietic elements and fat. The ratio of erythropoietic to myelopoietic centers was approximately one to three, and the maturation of cells was normal (Fig. 13*A*).

Hematopoiesis was markedly inactive in the athyroid animals. Medullary cavities were consistently much more fatty, with the number of blood-forming cells decreased 30 to 70% below normal (Fig. 12*B*). Although involving all bones, the change was particularly pronounced in the more distal appendicular skeleton. Thus, the midtibia of the athyroid animals was completely fatty. The marked reduction in cellularity was not associated with an alteration in the ratio of erythropoietic to myelopoietic centers or an arrest in maturation (Fig. 13*B*). Megakaryocytes were proportion-

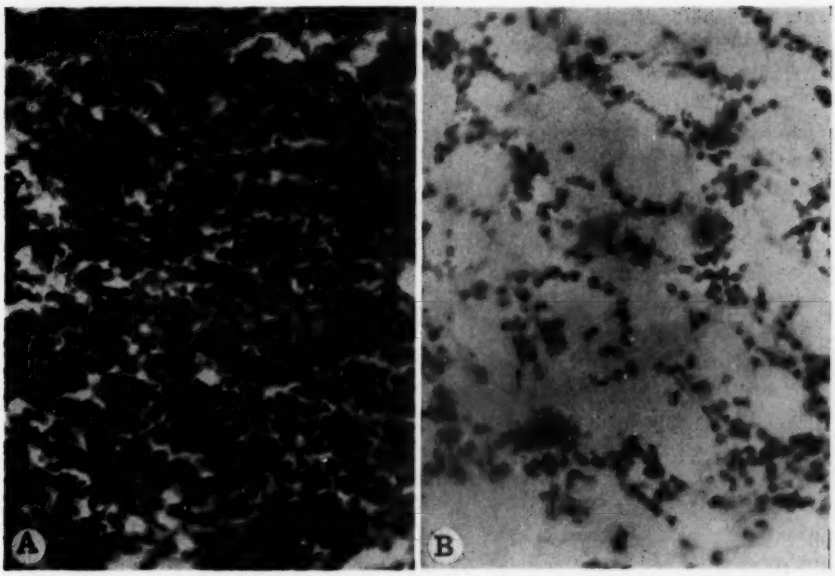

Fig. 13.—Medullary space—vertebra. *A*, normal—hematopoiesis is active, as indicated by the density of blood-forming cells. Several megakaryocytes are present. *B*, athyroid—the fatty marrow contrasts sharply with the normal. However, the ratio of erythropoietic to myelopoietic centers is unaltered. Two normal megakaryocytes are present.

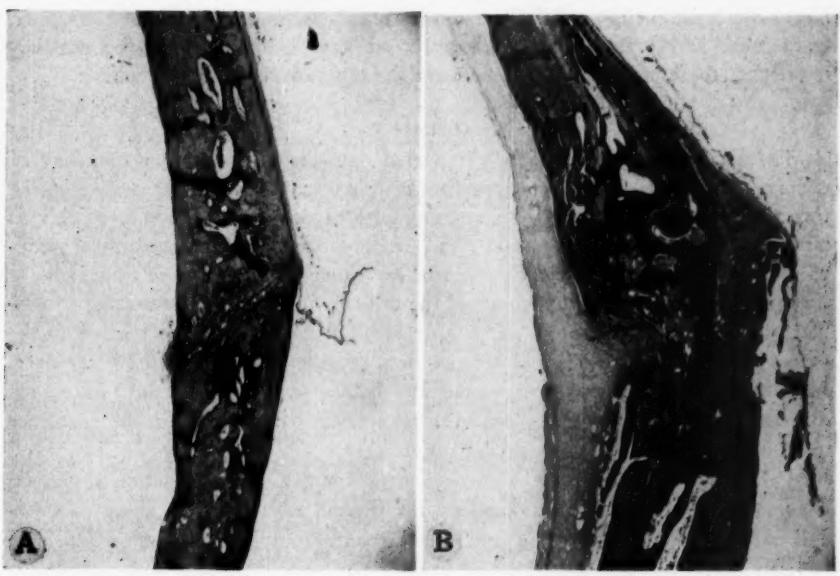

Fig. 14.—Cranial parieto-occipital synostosis. *A*, normal—the parietal and the occipital bone (below), united by a narrow zone of fibrous tissue, are in good alignment. *B*, athyroid—there is marginal malalignment of the parietal and occipital bones, the latter (below) overriding the former. Note periosteal elevation and ossification.

ately reduced but morphologically normal. Despite medullary hematopoietic inactivity, neither anemia, macrocytosis, nor leukopenia were observed during the period of study.

Skeletal alterations in athyrosis were usually manifestations of retarded development, although certain minor deformities were observed. One of the most prominent of these deformities was the formation of a palpable ridge along the cranial parieto-occipital suture line. This was the result of a partial overriding of the parietal bones by the occiput, with the inner table of the occiput in rough alignment with the outer tables of the parietals (Fig. 14*B*). The periosteum adjacent to this malunion was separated from the underlying bone. In the wedge-shaped zones formed between the elevated periosteum and the cortical surfaces were numbers of new bone trabeculae.

Other specific bony deformities usually described in human athyroids were insignificant. The relatively small epiphyses of major long bones exhibited no flattening or angulation. The age and postural weight distribution in the infant monkey probably accounted for the lack of such deformities.

Serial roentgen surveys revealed a striking and generalized delay in the pattern of maturation of the skull and the axial and appendicular skeleton in untreated athyroid animals.[5] In those treated with approximately 6 γ of *l*-thyroxine per kilogram per day, that condition remained unchanged, while in those receiving 20 γ per kilogram per day, a rapid rate of maturation commensurate with that found in normal animals was resumed. Crania of the athyroid animals maintained an infantile configuration (dolichocephaly), with persistence and accentuation of sutures. Prognathism was prominent due to the relative absence of growth by mandibular rami. Deciduous teeth, though well formed, did not erupt. Secondary centers of ossification in the axial and appendicular skeleton were delayed in their appearance. As they developed, these centers were of uniform density and remained unmolded.

COMMENT

There have been no previously reported data on the skeletal morphology of experimental athyrosis or hypothyroidism in primates. Experimental studies on the relationship between the thyroid gland and skeletal development have been carried out principally on guinea pigs and rats.|| In these smaller animals, surgical extirpation of the thyroid is frequently followed by regeneration of thyroid tissue and/or hypoparathyroidism. In order to avoid the critical and probably impossible experimental definition of effects of "varying degrees" of intrinsic hypothyroidism in the present study, complete thyroid ablation was considered necessary in all animals. Clinical and biochemical criteria supporting the diagnosis of "athyrosis" have been discussed. Present observations confirm that animals receiving I^{131} in the quantities described (2 mc.) were anatomically athyroid.

Parathyroid gland integrity was considered essential in the evaluation of skeletal changes in athyrosis. By all indications, I^{131} thyroid ablation in the infant monkeys was attended with functioning and intact parathyroid glands. Tetany failed to develop. Repeated determinations of urinary and serum calcium and phosphorus were constantly within the normal range following thyroid ablation.[2] In relation to total body weight, the size of the parathyroid glands of the athyroid animals

|| References 7-8.

was comparable to that of the normals. Of considerable interest was the cellular alteration of the parathyroid glands. With the prolonged interval between thyroid ablation and histological examination, it would be highly improbable that this alteration represented a residual I^{131} effect. It was established that the increased bone density of athyrosis was not the result of any coincidental impairment of parathyroid function, since bone density of athyroid animals became normal with optimal *l*-thyroxine therapy.[5]

There was retardation in skeletal development, involving both linear and circumferential growth, aging, and bony reconstruction. This applied, as well, to all types of ossification in both membranous and endochondral bones. No one phase of development was selectively retarded in a manner which would indicate a specific and direct effect of thyroid deficiency. It is true that there was variable degree of retardation as applied to the phases of skeletal development and the types of ossification. The retardation was most pronounced in delayed skeletal aging and bony reconstruction. Somewhat less affected was endochondral and membranous ossification, while periosteal ossification was least affected. These combined factors produced the more dwarfed, relatively broader, denser, and more infantile skeleton of the athyroids.

As has been pointed out, the various phases of development and types of ossification have certain morphological features in common. Of these, three were constantly observed and can be considered basic:

(*a*) The delay in cellular maturation: This was best demonstrated in the retarded transformation of columnar cartilage cells into hypertrophic cells (endochondral ossification) and of fibrous cells into osteocytes (membranous ossification).

(*b*) A decrease in the ratio of cells of extracellular substance: This was evident in epiphyseal cartilage, as well as cortical and trabecular bone.

(*c*) A decreased vascularity: This was most evident at zones of cartilagenous erosion, synosteal lines, and Haversian canals.

In seeking a correlation between these morphological changes and the known function of thyroid hormone, two potential mechanisms were considered. First, that such changes are mediated through other organ systems. Of particular importance are the other endocrine glands known to affect bone directly, i. e., the pituitary, parathyroids, adrenals, and gonads; second, that these changes are but a localized reflection of a generalized depression in metabolism. It has already been implied that lack of thyroid hormone does not produce a singular morphological alteration in bone, and, therefore, the effect of thyroid hormone is not direct and specific.

Alteration from normal in the pattern of hormonal elaboration by the adenohypophysis has been particularly implicated as a determinant of skeletal changes induced by thyroidectomy. Silberberg and Silberberg[7] suggested that the initial increase in epiphyseal cartilage in experimental hypothyroidism was the result of induced pituitary stimulation. However, the only pituitary substance known to be elaborated in increased amounts following thyroidectomy is thyrotropic hormone,[9] and in the absence of the thyroid, thyrotropic hormone has not been observed to influence bone. Other workers[11] have postulated that the pituitary alpha-cell suppression following thyroidectomy is related to decreased elaboration of growth hormone and that this is partially responsible for the growth deficit in athyrosis.

It is unlikely that hypopituitarism with respect to growth hormone is an important factor in athyroid dwarfing, in view of the marked refractoriness of thyroidectomized animals to that substance.[12]

Classically, effects of parathormone upon bone development have not been observed to be disassociated from its effects on calcium-phosphorus metabolism per se. As noted, calcium and phosphorus metabolism remained normal following thyroid ablation in these animals, and, it will be recalled, thyroxine alone effected a complete reversal in skeletal changes induced by that procedure.

A decrease in adrenal size has been observed in these and other animals following thyroidectomy,[13] but it has not been conclusively demonstrated to be a specific endocrine effect. More probably it is a direct response to the general metabolic depression of athyrosis. Under these conditions, adrenal functional alteration would be relative and, therefore, would not directly affect skeletal development. Thyroid ablation does not cause functional or morphological changes in infantile gonads, and it is, therefore, unlikely that a secondary effect on bone development is mediated through these organs.

A direct effect of thyroxine on bone, disassociated from its more classic and general function of catalyzing tissue respiration,[14] is unlikely. It is more probable that the skeletal features of athyrosis result from the generally reduced energy potential present in all tissues. With athyrosis, uncatalyzed respiratory enzyme systems effect a significantly reduced energy potential, only slightly above that necessary for maintenance of basic cellular function. The increased ratio of extracellular substance to cellularity may be related to this functional alteration. As observed in normal macaque infants, energy requirements of growth are extreme (18 ± 3 Cal. per gram of weight gain).¶ In athyrosis, this energy is unavailable, and a corresponding deficit of cellular growth and maturation occurs. This is manifest morphologically by retardation of cellular maturation and relatively reduced cellularity, a function of cell reproduction (growth). It is more probable that the principal function of thyroid hormone is to effect availability of that energy required for skeletal development, the rate of development being variable and intrinsic among various tissue sites. Bone development, as influenced by vascularity, is probably a related but secondary manifestation of the same process.

SUMMARY

A detailed study of skeletal morphology of normal and I^{131} thyroid-ablated infant rhesus monkeys is presented in conjunction with selected endocrine observations which (*a*) confirm the completeness of thyroid ablation in I^{131}- treated animals in whom functionally intact parathyroids were identified, and (*b*) which describe the secondary adenohypophyseal enlargement with beta-cell hypertrophy induced by thyroid ablation.

Skeletons of athyroid infant animals were dwarfed, relatively broad, and dense. There was a persistence of infantile configurations; epiphyseal lines and cranial sutures were broad, while secondary centers of ossification were underdeveloped.

Throughout cortical and medullary bone and in zones of ossification there was a delay in cellular maturation, a decreased ratio of cells to extracellular substance,

¶ Pickering, D. E.: Energy Dynamics of Growth in Infant Rhesus Monkeys, unpublished data.

and a decreased vascularity. Marked retardation in skeletal reconstruction was an additional general feature in athyroid animals. Hematopoiesis was generally retarded.

Morphological features indicate a generalized retardation of skeletal development, not only of skeletal aging but also of linear and circumferential bone growth and bony reconstruction. This retardation was not selectively confined to any one type or group of bones or to a specific form of ossification.

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HUMORAL ANTIBODIES AND INTRADERMAL REACTIONS TO CHEMICAL FRACTIONS OF HEMOPHILUS PARAPERTUSSIS

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AS A PART of a study of immunity in parapertussis, a survey of the serum agglutinin titers in a representative sample of infants and children was made. Previous observations by Miller,[1] in San Francisco, and by Flosdorf,[2] in Philadelphia, suggested that the finding of a significant number of persons with agglutinins against Hemophilus parapertussis indicated that the disease caused by this organism had occurred fairly frequently.

The present paper reports the titers of agglutinins for H. parapertussis and for H. pertussis in the serums of 531 patients, from birth through 14 years of age, admitted to the pediatric service of the Strong Memorial-Rochester Municipal Hospitals during the period from Jan. 1, 1951, to July 1, 1952. During this 18-month period, approximately 3,000 admissions occurred. No plan prevailed for the selection of serums to be tested, and they represent a random distribution in relationship to age and time of admission.

In addition to the survey of serum antibody, intradermal tests were made with "agglutinogen" fractions of the two organisms. Finally, the effects of immunization with H. parapertussis on the agglutinin titers and on the intradermal reactions were determined in 14 infants.

PROCEDURES

The serums, after separation from the clots, were stored in the icebox until tested, at about weekly intervals.

All of the antigen for the agglutination tests was prepared from a single strain of H. parapertussis (Treadway), which had been lyophilized immediately after isolation from a child with typical symptoms. It was fully identified by its cultural and serological characteristics. A suspension of organisms was prepared from the second transfer on a Bordet-Gengou medium of the reconstituted culture and standardized by means of a Klett-Summerson colorimeter to contain approximately 40,000,000 organisms per milliliter of a 1.7% sodium chloride solution, which was used to prevent the spontaneous clumping often observed when this organism is

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suspended in an 0.85% salt solution. The titers recorded are the final dilutions of serum after mixture with the antigen. Preliminary tests indicated that the results obtained with different strains of H. parapertussis varied only slightly; hence, the use of a single strain for these agglutinations was justified. The antigen for the agglutination tests with H. pertussis was prepared in a similar manner from a single strain (Sicca) with the exception that the suspension of organisms was made in 0.85% salt solution.

Intradermal tests were made with "agglutinogen" fractions of H. parapertussis (Treadway strain). Four preparations were used, designated as I, II, III, and S. Fractions I, II, and III were prepared by the method of Bondi and Flosdorf [3] from organisms grown, respectively, on a Bordet-Gengou medium, in a Cohen-Wheeler medium,[4] and in a slightly modified Cohen-Wheeler medium.[5] For Fraction S, the organisms were grown in the modified Cohen-Wheeler medium, harvested by centrifugation, and disrupted by sonic vibration with a Raytheon oscillator, Model S-102A. After removal of cellular debris by centrifugation, the "agglutinogen" was fractionated from the soluble portion by the procedure of Bondi and Flosdorf.[3] All of Fraction I and part of Fraction II were consumed in preliminary intradermal tests, on the basis of which a final dose of 0.1 ml. of either a 1 : 50 or 1 : 100 dilution in saline of Fraction II was selected for additional tests, as one that gave adequate, but not too severe, reactions in sensitive subjects. Fractions III and S were standardized also on the basis of their contents of total solids, of nitrogen, and of agglutinogen, as determined by the method of Flosdorf and Kimball.[6] The final solutions contained 2.8 mg. and 1.7 mg. of total solids, and 0.164 mg. and 0.087 mg. of nitrogen per milliliter, respectively. The agglutinogen contents of both were estimated to be 1,600 units per milliliter, which corresponds to 1.8 and 1.1 γ of total solids per unit, compared with a value of 3 γ given by Bondi and Flosdorf.[3] The skin test dose of each was 0.1 ml. of a 1:100 dilution in saline, which represented, therefore, 1.6 agglutinogen units, or one-sixth the amount used in analogous studies with pertussis agglutinogen.[7] This smaller dose of parapertussis agglutinogen was found by trial to be optimal for the purposes of the present investigation. On the other hand, the intradermal tests with pertussis agglutinogen were done with a commercial preparation* according to the directions of Felton and Flosdorf.[7]

Both Fraction III and Fraction S completely absorbed the agglutinin for H. parapertussis from antipertussis rabbit sera. Fraction S, but not Fraction III, also absorbed agglutinin for H. pertussis from rabbit antisera against either organism; its content of "H. pertussis agglutinogen" was 150 units per milliliter. Fraction III, therefore, was the more specific, antigenically.

Finally, immunization of rabbits by the intravenous injection of a series of six doses of either Fraction II or III (0.2, 0.2, 0.4, 0.6, 1.0, and 1.0 ml. of a 1 : 100 dilution) resulted in serum agglutinin titers of from 1 : 160 to 1 : 320 for H. parapertussis, but in no demonstrable agglutinins for H. pertussis.

Skin tests were performed by injecting 0.1-ml. amounts of the appropriate reagents intradermally on the volar aspect of the forearm, using a standard 1.0-ml. Luer syringe equipped with a 26-gauge needle. With each test of the H. parapertussis fractions, a simultaneous injection of pertussis agglutinogen was made on the opposite forearm for comparison. Reactions were observed and measured at the end of 24 hours. Only the diameter of the area of induration was recorded, for, in the case of pertussis agglutinogen, induration rather than erythema is the determinant factor in assessing the degree of immunity.[7] In classifying reactions resulting from the injection of pertussis agglutinogen, Felton and Flosdorf [7] used the following designations: 0 to 9 mm., susceptible; 10 to 19 mm., weakly positive immune, and over 20 mm., positive immune. In our study we have separated the reactions into four groups: 0 to 4 mm., 5 to 9 mm., 10 to 19 mm., and 20 mm. or greater.

COMMENT

Agglutinin Titers.—When the entire group of 531 subjects was arranged according to the agglutinative titers of the serums, it was noted (Table 1) that 38 (7.1%) exhibited titers of 1:320 or higher against H. parapertussis, as compared with 183 (34.4%) against H. pertussis. A titer of 1:320 is generally considered to be the level indicative of immunity.

* Supplied through the courtesy of the Research Division of Sharp & Dohme, Inc.

In the group of 88 subjects (Table 2), in whom there was a negative history of pertussis and of pertussis vaccine, only three had titers of 1:320 or higher against H. pertussis, and only one serum had this titer against H. parapertussis.

Eighteen patients had a positive history of pertussis but had never received vaccine. None of these had high titers against H. parapertussis (Table 2), and only two were positive against H. pertussis (1:320 or higher).

The largest group tested consisted of 273 serums from patients who had negative histories of whooping cough but had received pertussis vaccine at some time prior to testing. Of this group (Table 2), 15 (5.5%) had titers of 1:320 or higher against H. parapertussis, as compared with 121 (44.3%) against H. pertussis.

A fourth group included 38 patients who had had both whooping cough and an injection of pertussis vaccine. Five (13.2%) had titers of 1:320 or higher against H. parapertussis, compared with 14 (36.8%) against H. pertussis.

TABLE 1.—*Serum Agglutinin Titers in a Group of 531 Routine Pediatric Admissions*

	Distribution of Cases According to Titer										
Antigen	0	10	20	40	80	160	320	640	1,280	2,560	% >320
H. Pertussis	144	5	32	34	83	50	78	83	12	10	34.4
H. Parapertussis	202	46	73	57	75	39	24	7	6	1	7.1

TABLE 2.—*Serum Agglutinin Titers Against H. Pertussis and H. Parapertussis According to the History of Pertussis and of Previous Injection of Pertussis Vaccine*

History			Range of Titers					
			H. Pertussis			H. Parapertussis		
WC*	VAC†	No. Tested	0	10-160	>320	0	10-160	>320
0	0	88	59	26	3	46	41	1
0	+	273	44	108	121	95	163	15
+	0	18	10	6	2	8	10	0
+	+	38	7	17	14	13	20	5

* WC indicates whooping cough.
† VAC indicates vaccination against H. pertussis.

From these results, it is evident that an attack of whooping cough in the absence of immunization against H. pertussis did not increase the incidence of immunity level titers against H. pertussis materially above that found in the reference group. Similarly, the incidence of such titers in the immunized groups was essentially the same regardless of experience with the disease. This level of agglutinin against H. parapertussis seldom occurred in the nonimmunized children and occurred to only about one-seventh the extent found against H. pertussis in the immunized groups, regardless of a history of pertussis. These results indicate that agglutinative titers are not reliable indicators of the prevalence of infection by these two organisms. The increased incidence of intermediate titers (1:10 to 1:160) and of high titers (1:320 and above) seemed to be attributable to the administration of H. pertussis vaccine.

Of special interest, therefore, was a small group of 14 infants with negative histories for whooping cough who were immunized with vaccine containing both H. parapertussis and H. pertussis. The vaccine, prepared by adding heat-killed H. parapertussis (Treadway strain) to a commercially prepared alum-precipitated

diphtheria-pertussis-tetanus vaccine, contained approximately 20,000,000 of each organism per milliliter. The infants received three intramuscular injections (0.5 ml. each) of this vaccine at monthly intervals, beginning at 6 weeks of age. Preinjection titers of the members of this group could not be obtained, but for comparison the titers of a similar group of 20 nonimmunized young infants were available, as indicated in Table 3. Titers of the immunized infants were determined approximately one month after completion of the course of vaccine injections. It is evident that the vaccine stimulated a good antibody response, for 7 of the infants developed titers of 1:320 or higher against H. parapertussis, and 11 did so against H. pertussis.

TABLE 3.—*Agglutinin Titers and Skin Reactions in Nonimmunized and in Immunized Infants Under Two Years of Age*

Nonimmunized					Immunized*				
	Agglutinin Titer		Skin Tests			Agglutinin Titer		Skin Tests	
Patient	H. Pert.	H. Para.	Pert., Mm.	Para., Mm.	Patient	H. Pert.	H. Para.	Pert., Mm.†	Para., Mm.
T. W.	0	10	0	0	J. A.	320	320	..	15
D. A.	40	20	1	3	G. B.	80	160	20	30
R. McW.	0	0	0	3	A. E.	640	640	..	5
F. N.	0	0	5	2	J. E.	320	320	..	20
E. G.	20	0	2	2	G. F.	80	80	10	12
V. C.	0	0	1	0	F. H.	320	160	20	6
J. F.	0	8	0	0	J. H.	320	80	30	20
B. M.	0	20	0	0	W. J.	320	40	..	20
J. D.	0	20	5	3	J. H.	80	80	..	40
M. H.	20	10	5	5	F. P.	320	80	..	20
K. A.	0	10	0	0	F. R.	640	320	10	8
R. P.	0	0	3	0	D. S.	1,280	320	..	20
R. W.	0	0	0	0	S. C.	640	640	10	30
D. C.	40	80	0	0	I. V.	640	640	..	20
F. H.	0	0	3	0					
L. C.	20	20	3	1					
P. S.	20	20	3	1					
I. S.	20	20	0	0					
D. McC.	20	10	3	0					
L. E.	0	0	3	0					

* Immunized against both organisms.
† .. indicates not done.

Skin tests.—With each parapertussis fraction, the type of reaction observed was remarkably similar to that obtained with pertussis antigen, namely, a tuberculin type of erythema with or without induration. The maximal intensity occurred between 24 and 48 hours. In certain instances, induration occurred with a minimal degree of erythema. No difference was detectable in the efficacy of the three fractions tested (Table 4). In a group of 47 subjects who, according to their histories, had had neither pertussis nor vaccine, 15 were tested with Fraction II, 21 with Fraction III, and 11 with Fraction S. All except five gave reactions less than 5 mm. in diameter. The incidence of reactions was much increased by immunization with pertussis vaccine. In a group of 98 such patients whose histories were negative for whooping cough, 30 gave reactions of 5 mm. or larger, of which 15 were larger than 10 mm. and 3 were larger than 20 mm.

Even more striking was the effect of immunization of a group of infants less than 2 years of age having negative histories for whooping cough with the vaccine con-

taining both H. pertussis and H. parapertussis (Tables 3 and 4). Only one of the 20 nonimmunized infants gave even as great a reaction as 5 mm., whereas all of the 24 immunized infants did so. Of these, 18 reactions were larger than 10 mm., and

TABLE 4.—*Skin Reactions to Different Fractions of H. Parapertussis*

History				Skin Reaction, Mm.			
WC*	VAC†	Fraction	No.	0-4	5-9	10-19	20
0	0	II	15	13	2	..	..
		III	21	18	3	..	..
		S	11	11	0	..	..
0	+‡	II	40	35	4	1	..
		III	39	20	7	9	3
		S	19	13	4	2	..
0	0	III	12	11	1	..	..
(<2 yr. of age)		S	8	8	..	..	..
0	++§	III	13	..	3	2	8
(<2 yr. of age)		S	11	..	3	6	2

* WC indicates whooping cough.
† VAC indicates vaccination against H. pertussis.
‡ + indicates H. pertussis vaccine alone.
§ ++ indicates H. pertussis and H. parapertussis vaccine.

TABLE 5.—*Correlation of Skin Reactions to Agglutinogens of H. Pertussis and H. Parapertussis with the History of Pertussis and of Previous Injection of Pertussis Vaccine*

		Size of Reaction, Mm.							
		Pertussis Agglutinogen				Parapertussis Agglutinogen			
History				>5 Mm.				>5 Mm.	
WC*	VAC†	No.	0-4 Mm.	No.	%	No.	0-4 Mm.	No.	%
0	0	44	30	14	32	47	42	5	11
0	+	99	21	78	79	98	68	30	31
+	0	9	5	4	44	9	7	2	22
+	+	21	11	10	48	20	17	3	15

* WC indicates whooping cough.
† VAC indicates vaccination against H. pertussis.

TABLE 6.—*Relationship of Skin Tests to Homologous Agglutinin Titers and Expected Number of Immunes* *

	Size of Skin Reaction					
	Pertussis Agglutinogen			Parapertussis Agglutinogen		
Agglutinin Titer	0-4 Mm.	>5 Mm.	Expected No. Immune†	0-4 Mm.	>5 Mm.	Expected No. Immune†
0	6	9	10	25	2	18
10-160	14	43	45	40	25	51
320	1	26	27	3	1	4

* Subject had been vaccinated against H. pertussis but had never had the disease.
† Expected number immune calculated according to Sako.[3]

10 reactions exceeded 20 mm. Two of three infants who had been infected previously with H. parapertussis reacted to Fraction III.

Since an adequate number of parapertussis cases was not available, a comparative study was made of the skin reactions to pertussis and paratussis agglutinogens in relationship to the history of previous attacks of whooping cough and to the previous

injection of pertussis vaccine. With these categories as bases for comparison, the results of the skin tests are recorded in Table 5. The results resemble those observed in agglutination tests (Table 2). A considerable proportion of patients who had neither had whooping cough nor received the vaccine gave skin reactions to the agglutinogens. This incidence was sharply increased by immunization, but, paradoxically, was increased to a lesser degree by an attack of whooping cough, whether preceded by immunization or not. As was presumably to be expected, the incidence of reactions to parapertussis agglutinogen was lower throughout.

In Table 6, the data are arranged to show the relationship between the skin reactions and the agglutinative titers for the homologous organisms in subjects who had previously received pertussis vaccine but had never had the disease. On the basis of these results, we have adopted provisionally a reaction greater than 5 mm. as indicative of either partial or complete immunity, for in the case of H. pertussis it agrees closely with the agglutinative titer as a basis for calculating the expected number of immune vaccinated subjects. Sako [8] found that when immunized children were exposed to pertussis, the degree of resistance to subsequent exposure was reflected by the serum agglutinin titer at the time of exposure. For instance, even when the titer was 0, 66% escaped the disease, but when it was 10 to 160, 79% escaped (interpolated from author's data), and when the titer was greater than 320, all escaped.

When the number of expected pertussis immunes calculated from the agglutinative data (Table 6) is compared with the number of subjects having skin reactions greater than 5 mm. to pertussis agglutinogen, we note the agreement as follows:

Agglutinin Titer	Immune by Titer	Immune by Skin Test
0	10	9
10-160	45	43
320	27	26

However, a large discrepancy exists when similar values are calculated from the parapertussis data (Table 6). The number of expected immunes estimated by the skin test is much smaller than that calculated on the same basis as above from the agglutinin titers. No doubt many of the increased titers against H. parapertussis resulted from immunization with pertussis vaccine and would have been much lower had the serums been previously absorbed with H. pertussis. Moreover, some of these children may have had inapparent attacks of parapertussis.

SUMMARY

In a series of 531 routine admissions to a general pediatric service, 328 (61%) had demonstrable serum agglutinins against H. parapertussis. Thirty-eight (7%) had titers of 1 to 320 or higher, whereas 183 (34%) had titers in this range against H. pertussis. These data were correlated with the history of pertussis and with the previous injection of H. pertussis vaccine.

Certain chemical fractions prepared from H. parapertussis revaled-immunological characteristics similar to those of H. pertussis agglutinogen. They absorbed the agglutinin from rabbit antiserum against H. parapertussis and induced the formation of specific agglutinin when injected into rabbits.

When injected intradermally, these fractions gave reactions of erythema and induration in infants previously injected with H. parapertussis vaccine but gave no reactions in nonimmunized infants. Half of the immunized infants developed serum agglutinin titers of 1:320 or higher against H. parapertussis.

In the general series, there was a considerable incidence of skin reactions to the parapertussis fractions which was greater in those children who had had whooping cough but which was highest in the group that had been immunized with H. pertussis vaccine.

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ACUTE HYPERVITAMINOSIS A OF THE INFANT

Its Clinical Manifestation with Benign Acute Hydrocephalus and Pronounced Bulge of the Fontanel; a Clinical and Biologic Study

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CHRONIC hypervitaminosis A accidents are now well known, through the works of Rodahl and Moore and Josephs, and especially through the mainly experimental observations of Toomey and Morisette and, later of Rothman and Leon. There are various publications on this subject in the medical literature.

Our purpose is to draw attention to the acute incidents which may follow the administration of very large quantities of vitamin A in the infant. These incidents are especially characterized by acute hydrocephalus, with spontaneous and intensive bulging of the fontanel, frequent vomiting, agitation, or insomnia, and this without any meningeal sign or disorder in the general status. The disturbances begin 12 hours after ingestion of the drug and end 24 to 48 hours later, spontaneously or after lumbar puncture.

Since we first described, in February, 1951,[1] the syndrome of acute and benign hydrocephalus in the infant following the ingestion of a large amount of vitamin A, the observation has been confirmed by many pediatricians. Some of them remembered infants presenting extreme bulging of the fontanel, vomiting, and normal temperature, but with the cause of the disorder unknown. Informed by our observations, they conducted a written or oral inquiry of the families, and they were able to retrace the ingestion, 24 hours before the incident, of a large dose of vitamin A, plain or associated with vitamin D. Such are the cases reported by S. Thieffry (Paris), in dizygotic twins, and by M. L. Jammet (Paris), l'Hirondel (Caen), and Cluet Garcia [2] (Barcelona). Finally, after our communication, many French and foreign pediatricians observed the syndrome as we described it—in particular, Fleury [3]; Vonderveit, in France; Montero Rodriguez,[4] in Spain; Caruana and Hamza,[5] in Tunisia; Demoulin [6] and Hooft, in Belgium, and Knudson and Rothman [7] (Dr. Mary Mulloy's case), in the United States.

I. ACUTE HYDROCEPHALUS FOLLOWING INGESTION OF LARGE QUANTITY OF VITAMIN A ASSOCIATED WITH VITAMIN D

We shall here report three cases we presented on Feb. 20, 1951, at the Society of Pediatrics in Paris.

CASE 1.—B. Gilles, aged 3½ months, weighing 5,600 gm., on July 7, 1949, vomited at 7 p. m. the feeding he had just drunk. He was pale and fell asleep very soon and did not awaken at

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10 p. m. for his feeding, although he usually had a good appetite. On the next day the child was gay and drank well, but he was still pale, and the mother noticed a bulge of the fontanel.

The child was brought to the hospital; he was strictly afebrile and looked normal, but his anterior fontanel was very protruding and distended, even when he sat up, the fontanel resembling the head of a cap mushroom on the cranial surface. The neck was flexible, and there was no neurological anomaly. The fundus oculi was normal, and the ear examination revealed no abnormality. The lumbar puncture showed a clear fluid, with 1.4 cells per cubic millimeter and 25 mg. of albumin per 100 cc.

The next day the child seemed to have recovered; the fontanel was rather depressed, but one could notice edema at the point of lumbar puncture, proving the persistence of a subcutaneous flow of the spinal fluid. The condition had returned to normal on July 10.

The history showed that on the morning of July 7 the infant had drunk in his bottle the contents of an ampule which had contained a large amount of vitamins A and D.

Case 2.—I. Jean-Louis, aged 7½ months, on Sept. 27 presented cerebral vomiting at 1 and 4 p. m., soon after having drunk his feeding. During the afternoon he was very sleepy, but at night he played and smiled normally.

On Sept. 28 this child, of 7,000 gm., presented a very prominent bulge of the fontanel, more conspicuous when he cried and without any pathological sign.

The lumbar puncture showed a clear fluid containing 1.8 cells per cubic millimeter, and 15 mg. of albumin, 80 mg. of sugar, and 730 mg. of chlorides per 100 cc.

The day ended well, and the next day the child had recovered completely.

Investigations showed that the child had taken an ampule containing the same large amount of vitamins A and D as in the preceding case.

Case 3.—M. Claudine, 3 months old, on Jan. 20 presented projectile vomiting 10 minutes after having drunk her feedings at 7 and 10 a. m. The child's father noticed that the fontanel was distended and protruding. In the afternoon she took her feedings but had a diarrheal stool. The temperature was normal.

On Jan. 21, the child vomited at 7 a. m., but she was gay, had good color, and was smiling. The fontanel was easily seen, protruding and tense. There was no meningeal or neurological sign.

The blood pressure was 85/40. The lumbar pressure, measured with Claude's manometer in the lateral position, was 31 cm. of water; after jugular pressure it increased to 42 cm., and on abdominal pressure, to 56 cm. of water.

The spinal fluid was clear and contained 2.2 cells per cubic millimeter and 35 mg. of albumin, 60 mg. of glucose, and 700 mg. of chloride per 100 cc.

On the night of Jan. 21 the fontanel was still a little distended and prominent, but the child retained her feedings. The next day there was no disturbance.

The child had never been ill, except for a slight cold the previous week. On Jan. 19, at 7 p. m., she took with her feeding the contents of an ampule of the same composition as those ingested by the other two children, the three ampules coming from the same pharmaceutical laboratory.

Claudine retained this feeding and the following one, and it was 12 hours later that the first prominent vomiting occurred.

These three children had all received 12 to 24 hours before the disorders an ampule of Vitadone Forte, containing 350,000 units of vitamin A and 7.5 mg. of vitamin D_2 (calciferol), that is, 300,000 units.

We managed to reproduce the same syndrome in two hospitalized infants, 4 and 7 months old, after ingestion of this same drug. We also observed an acute hydrocephalus produced by hypervitaminosis A in a 2-month-old infant who received nose drops containing 50,000 units of vitamin A, supplemented with vitamin D. The summary of the case follows.

Case 4.—R. Alain, aged 2 months, weighing 4,700 gm., presented on Oct. 20, 1950, a prominent bulge of the fontanel, without any vomiting, discomfort, or increased temperature. The lumbar puncture showed a clear fluid containing 2.8 cells per cubic millimeter and 25 mg. of albumin per 100 cc.

On Oct. 24, the child seemed cured.

Four weeks previously he had had a slight rhinopharyngitis, which was initially treated with a product containing penicillin. During the preceding week, he had been given nose drops of a preparation containing 50,000 units of vitamin A per gram and vitamin D. The child received 3 drops in each nostril, i. e., 6 drops four times daily, which amounts to about 1 gm. This totaled in six days a large quantity, of approximately 300,000 units, similar to the dose received by our other patients.

The fact is known that the pituitary mucosa is an excellent way of absorption for certain drugs, not excluding the possibility that a certain amount of the oily substance instilled in the nostrils might have been swallowed, penetrating the gastric passage.

II. ACUTE HYPERVITAMINOSIS A IN THE INFANT

In the previous cases, the role of vitamin A seems significant to us. Excess of vitamin D, well known from the works of Professor Debré and his collaborators, Thieffry and Brissaud, produces quite different effects. Nevertheless, the addition of vitamin D, even in very small quantity, to vitamin A, as it occurred in our preceding case, does not necessarily validate our observation.

We have therefore studied the result of administration of plain vitamin A to the infant, and in three cases out of six we managed to reproduce the acute hydrocephalus.

We shall report only one of these cases here.

Case 5.—C. Joel, 4 months, was treated in our service beginning Dec. 12, 1951, for purulent staphylococcal pleuritis, which was cured, but he presented a periscissural softening, his fontanel was wide and normally tense.

On March 5, at 5 p. m., the child ingested an ampule containing 350,000 units of natural vitamin A.

On March 6, at 6 a. m., the nurse that fed him, who was not aware of the ingestion of the drug, noticed that the fontanel was bulging and formed a knob on the child's head; the child vomited after he drank. At 8 a. m. the bulging was considerable; there was no meningeal sign. On March 7, the fontanel was still a little tense. On March 8, all abnormalities had disappeared.

The child vomited only once, but, although the child's weight increased regularly, there was a slight loss of weight on March 6 and 7.*

Vitamin A alone, given orally and in very great dosage, is therefore the cause of this unexpected and transitory incident.

In our subsequent studies, we continued to use plain vitamin A, and we systematically observed the status of the fontanel, the cerebrospinal fluid pressure, the fundus oculi, and, especially, the blood vitamin A level. Several times we reproduced the same disturbances in infants, from the age of 24 days to 15 months.

The precise clinical study of six infants who presented disorders after ingestion of a single dose of 350,000 units of vitamin A induces us to describe a special syndrome characterized by the signs to be noted.

1. *Functional Disorders.*—We noticed 12 to 24 hours after the ingestion, almost always, repeated projectile vomiting, twice, cerebral vomiting and diarrhea, and

* With other infants, we proceeded exactly in the same way, but using synthetic vitamin A instead of the natural vitamin; yet we could not reproduce the syndrome. Neither could we reproduce it with subcutaneous injections of natural vitamin A (60,000 to 90,000 units).

usually, restlessness, discomfort, insomnia, or drowsiness. Four infants showed a rise in temperature to 102.2 F. (39 C.); most of them did not gain weight for 48 hours; one of them even lost weight.

The disorders were, however, not proportional to the severity of the hydrocephalus; they perhaps were even inversely proportional; in fact, the child whose fontanel was most bulging had no disorder whatsoever.

2. *Clinical Study.*—We insist on the isolated character of the distended fontanel, which in the most typical cases produces a proper mushroom-like protuberance on the child's head, but there is no meningeal sign or any neurological anomaly. The blood pressure is not modified.

We have systematically studied the cerebrospinal fluid, and it appeared chemically and cytologically normal. The study of the spinal fluid tension was more interesting. Measured with Claude's manometer, the child being in lateral position and not crying, the fluid tension showed values from 15 to 23 cm. of water, and from 22 to 30 cm. after jugular pressure. In another group of infants, not receiving vitamin A, we found under the same conditions the following values: 11 to 13 cm., and 22 to 23 cm. after jugular pressure.

This slight hypertension of the spinal fluid is not proportionate to the height of the tension of the fontanel, but after evacuation of a certain amount of fluid there is a marked reduction of the bulge.

In these six infants, we systematically studied the fundus oculi and the electroencephalogram, without noticing any alteration. Likewise, there was no modification of the prothrombin rate.

3. *Chemical Study.*—Much more interesting was the measure of plasma vitamin A absorption rate, which we studied through Carr and Price's color test.†

For infants of less than one year, the level was, on an empty stomach, from 75 to 132 I. U., the average for six children being 102 I. U. In opposition to Mr. H. Aron's statements, the individual variations seemed to us to be proportionate to the alimentary diet and to the drugs taken by the children. In fact, the highest level (132 I. U.), was observed in a case of cured rickets.

Six hours after ingestion of the drug, the values reached 400 to 714 I. U.; the average value for the six children was 513 I. U. The increase seemed proportionate to the values at the start and reached five times that value. A few exceptions, however, were noticed, and they certainly pertained to different individual capacities of absorption and assimilation.

Twelve hours later, the values fell to about 170 and 353 I. U., that is, to two to three times the value at the start. It should be noticed that the most bulging fontanels are not accompanied by the highest values.

In a second series of six children, of less than 2 years of age, but whose fontanels were closed, the values at the start were 110 to 170 I. U., or an average of 140 I. U.

Six hours after ingestion, they reached 308 to 1,060 I. U., or an average of 690 I. U., i. e., five times the initial value. Twelve hours later, they dropped to values between 160 and 297 I. U.

Altogether, these values were higher than those of the infants.

We can add that we never found vitamin A in the cerebrospinal fluid.

† Miss Larrue and Mr. Chaix assisted with this test.

III. COMMENT AND EXPERIMENTATION

Acute hydrocephalus is, therefore, certainly produced by oral ingestion and absorption of a large amount of vitamin A. This is in connection with an excessive secretion of cerebrospinal fluid, evidenced by the increase of cerebrospinal fluid pressure. The hydrocephalus develops in parallel with the increase of vitamin A, but with a few hours' delay.

The connection between the spinal fluid and the vitamin A absorption rate are well known from studies by the veterinarians.[8] But, to our great surprise, it is hypovitaminosis which accompanies an excess of cerebrospinal fluid pressure. This fact seems so consistent that Canadian veterinarians rely on an increase of the spinal fluid pressure to reveal a hypovitaminosis A, and to treat it in time, in certain breeds of calves.

We succeeded in reproducing the syndrome of acute hydrocephalus ‡ in puppies from 3 to 4 months old.

One of them, weighing 4,000 gm., received an ampule of 350,000 units of vitamin A by mouth. It showed a very distinct tension of the fontanel. The initial level of plasma vitamin A was 310 I. U.; 6 hours later it was 1,700 I. U.; 12 hours later it fell to 850 I. U.

Two other puppies took only the oily solvent (vitamin A destroyed); they showed no modification.

Two other puppies received during three days 100,000 units of vitamin A a day, and they showed no disorder.

In the dog, as in the human being, vitamin A produces an acute and transitory hydrocephalus, provided one gets a massive and rapid absorption, expressed by an important increase in plasma vitamin.

SUMMARY

Our clinical observations and our work on infants and animals convinces us that the acute hydrocephalus, with intensive bulge of the fontanel, produced by the rapid absorption of vitamin A is a transitory and harmless disorder in both its immediate and its remote prognosis.

It seems to us, however, quite harmful to use this treatment in such excessive dosage. On our request, this drug is now being prepared in the concentration of 70,000 units of vitamin A and 2 mg. of vitamin D, and in this dosage it has thus far been perfectly tolerated.

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Progress in Pediatrics

NEONATAL JAUNDICE AND KERNICTERUS

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THE PURPOSE of this paper is to examine critically the available data bearing on the pathogenesis of kernicterus. During the past decade and a half, knowledge of the etiologic importance of incompatibility between the blood groups of the fetus and the mother has expanded rapidly. Nevertheless, sporadic reports of an association between jaundice and kernicterus in infants without hemolytic disease have been published.* The work of Zuelzer and Mudgett [1] and that of Aidin, Corner, and Tovey [2] require special mention. Their data indicate that, in absolute numbers, kernicterus is probably more commonly a complication of physiologic jaundice † than of isoimmunization. Systematic attempts to correlate the jaundice and the complications of these two forms of neonatal retention icterus are conspicuous by their paucity.‡ In the present communication, we shall first present additional evidence bearing on the lack of an obligatory association between kernicterus and hemolytic disease. Subsequently, pertinent data discovered in the literature will be appraised in the light of the conclusions suggested by the body of evidence.

ORIGINAL OBSERVATIONS

Within and about the city of Hiroshima, Japan, from April, 1948, to Aug. 31, 1952, a total of 732 autopsies were performed upon stillborn and newborn infants dying up to and including the second postnatal week. Almost all of the infants were born dead or died at home and were brought to our laboratory through the agency of the Midwives Association of Hiroshima. The subjects represent about 50% of all infants of this category dying during this period.

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* References 1-9.

† There will be objections to the use of the term "physiologic jaundice" in connection with a phenomenon which may terminate in utterly "unphysiologic" cerebral damage. We have struggled without success to find a satisfactory substitute for the term. Wide ranges of variability are observable in the jaundice which results from the hepatic immaturity of normal newborn infants. That, occasionally, the extreme reaches of a normal variant may be harmful to certain tissues must be accepted until knowledge has been amplified or a more suitable descriptive word coined.

‡ References 10 and 11.

The governing principle in obtaining the material was a desire to investigate as many newborn deaths as possible, irrespective of exposure or nonexposure of the parents to the atomic bomb. Thus the material is, in effect, as complete a sample as could be obtained.

Of the 732 cases, 13 (1.7%) revealed kernicterus (Tables 1 and 2). This overall figure does not reflect the real incidence of the lesion, since from April, 1949, to Feb. 6, 1951, only 1 case was recognized, while between Feb. 6, 1951, and Aug. 31, 1952, 12 cases were recorded. During the calendar year of 1951, among 218

TABLE 1.—*Historical Data*

Case No.	Sex	Gestation, Wk.	Age, Days	Preceding Siblings	Mother, A-Bomb Exp.	Father, A-Bomb Exp.	Mother, Previous Transfusion	Duration of Jaundice, Days
1	M	40	7	1. 8 yr.,† sepsis 2. 13 yr.,† A-bomb 3. L. & W. 4. 8 mo.† 5. L. & W. 6. 1 yr.,† A-bomb 7. L. & W.	+	+	0	4
2	M	32	2	1. 13 wk.,† s. a. 2. 3 days †	—	+	0	1
3	F	36	9	1. L. & W. 2. Stillbirth, 28 wk.†	+	—	0	3
4	M	30	7	1. L. & W. 2. 8 wk.,† s. a. 3. 12 wk.,† s. a.	—	—	0	1
5	F	33	12	1. L. & W. 2. L. & W. 3. 12 wk.,† s. a.	+	—	0	9
6	M	32	7	1. 20 wk.,† s. a. 2. 1 day †	—	—	0	4
7	F	28	7	1. 12 wk.,† s. a.	—	—	0	2
8	F	34	8	1. L. & W. 2. † a. a.	—	—	0	3
9	F	39	13	1. 48 days,† severe jaundice 2. L. & W. 3. a. a.†	—	—	0	11
10	M	42	3	1. 9 wk., s. a.	—	—	..	..
11	M	41	5	?	+	—	..	..
12	M	36	9	1. 9 wk.,† a. a.	+	—	..	6
13	M	31	13	1. L. & W. 2. L. & W. 3. L. & W. 4. L. & W. 5. 12 wk.,† s. a.	+	+	..	10

† indicates died; L. & W., living and well; s. a., spontaneous abortion; a. a., artificially induced abortion; +, exposed to A-bomb; —, not exposed to A-bomb; ?, not known.

infant autopsies, 7 (3.2%) instances of kernicterus were recognized, and during the first eight months of 1952, there were six cases (3.4%) among 178 such autopsies. On the basis of the two years' experience, the statistical estimate of the incidence of kernicterus among the newborn and stillborn infants in Hiroshima and its immediate environs is 3.3 ± 0.9%.

Blood from both parents of four of our subjects was sent to the United States Army 406th Medical General Laboratory,§ in Tokyo, for blood group determinations and the performance of indirect Coombs's tests upon the maternal sera. Completely negative results were obtained, insofar as isoimmunization is concerned. With the arrival of a skilled hematologist (W. C. M.) in the Atomic Bomb Casualty Com-

§ Dr. J. J. Stein and Col. R. P. Mason assisted in this study.

mission itself, similar but more extended procedures were carried out with the same results (Table 3). Since no blood specimens were available from the infants, serological investigation for maternal isoimmunization was carried out as follows:

1. Using the mother's serum against the husband's cells (in which the husband was either Group O Rh + or of the same blood group as the mother), direct agglu-

TABLE 2.—*Pathologic Data*

Case No.	Jaundice	Weight, Gm.			Erythropoiesis		Hemosiderin		Liver Bile Thrombi	Gmelin Test, Brain
		Body	Liver	Spleen	Liver	Spleen	Liver	Spleen		
1	+	2,595	155	12	+	±	—	—	—	—
2	++	2,100	72	2.5	—	±	+	++	—	..
3	+++	1,465	64.5	2.5	—	—	++	+++	—	..
4	—	1,070	36	5	±	++	—	+	—	—
5	++	1,600	76	6.5	±	+	+	+++	+	—
6	+	1,320	48	4.5	—	+	+	++	—	..
7	+++	820	35.5	5.5	—	—	—	+	—	..
8	+++	1,540	67.5	4.2	+	+++	+++	++	+	..
9	+++	2,810	113.5	12.5	±	±	++	+++	+	+
10	+++	2,300	145	10	+	+	+	+	++	..
11	+++	2,850	142	19.8	+	—	++	+	—	+
12	++	2,000	99.6	6.5	+	+	++	++	+	+
13	++	1,270	59.4	5.0	—	—	+++	+++	+	+

TABLE 3.—*Blood Grouping and Serological Tests for Maternal Isoimmunization*

Case No.	Blood Groups		Indirect Coombs's Test, Mother's Serum		Titration, Mother's Serum in AB Serum and Normal Saline	
	Mother	Father	Father's Cells	Test Cells	A Cells	B Cells
1	O Rh+	A Rh+	.....	Neg.	Not increased	....
2	B Rh+	AB Rh+	.....	Neg.	Not increased	....
3	O Rh+	A Rh+	.....	Neg.	Not increased	....
4	O Rh+	A Rh+	.....	Neg.	Not increased	....
5	A Rh+	A Rh+	Neg.	.....	.....	....
6	B Rh+	B Rh+	Neg.	.....	.....	....
7	AB Rh+	AB Rh+	Neg.	.....	.....	....
8	A Rh+	A Rh+	Neg.	.....	.....	....
9	A Rh+	O Rh+	Neg.	.....	.....	....
10	A Rh+	O Rh+	Neg.	.....	.....	....
11	O Rh+	O Rh+	Neg.	.....	.....	....
12	O Rh+	A Rh+	.....	Neg.	Not increased	....
13	O Rh+	O Rh+	Neg.	.....	.....	....

tination tests, with saline and serum-suspended husband's cells, and the indirect Coombs's test, using the husband's cells, were negative in the eight cases tested.

2. In five cases, the husband had red cell antigen A, while the wife was A negative. In these five cases, the maternal serum was tested against a panel of red cells containing nearly all the known red cell antigens (Rh, MNS, P, Kk, JK^a, Fy^a, Le^b, Le^a). Direct agglutination and indirect Coombs's tests were all negative. To rule out immune anti-A antigen, a titration of the maternal serum with saline and AB serum, employing the husband's A cells suspended in saline and in AB serum as test cells, failed to reveal increased titers of anti-A beyond the normal range in

either saline or AB serum. The unfortunate fact that the AB serum was not first neutralized with AB substance may cast some doubt on the validity of conclusions in this segment of the data, but the over-all inferences are not thereby invalidated.

Before any of the serologic procedures (Table 3) were carried out, it was evident that hemolytic disease of the newborn could not be a factor in the production of the kernicterus for several reasons: The incidence of Rh negativity in the Japanese is 0.44%.[12] In 1951, 6,699 births were registered within the municipal limits of Hiroshima. If, during that year, the Rh-negative Japanese mothers had all borne living infants with hemolytic disease, and if 15% had developed kernicterus, of which 70% died, there would have occurred, among the 6,699, three fatal cases of hemolytic disease. Since fewer than 5% of the Rh-negative mothers give birth to infants with hemolytic disease, and only those who survive 24 hours or more develop kernicterus, it is reasonable to conclude that the observation of seven cases of kernicterus in only 50% of the newborn fatalities is highly significant evidence that hemolytic disease of the newborn was not an important factor in the pathogenesis of our cases. In addition, the pathologic anatomy (Table 2) was not characteristic of hemolytic disease.

GENERAL COMMENT

Because kernicterus is associated with both physiological jaundice and the icterus of hemolytic disease, it would appear desirable to examine the genesis of these two forms of neonatal jaundice.

The genesis of physiologic jaundice was reviewed by Weech,[13] who concluded that physiologic jaundice was largely due to retention by the immature liver of physiologically produced bilirubin, and, consequently, "the behavior of the infant with respect to bilirubinemia is already largely predetermined at the time of birth." The highest serum bilirubin among 94 term infants was 26.2 mg. per 100 cc. Weech, however, mentioned one case in which the serum bilirubin reached 40 mg. per 100 cc., with no demonstrable anemia or hemolytic disease.‖ Concerning the origin of the bilirubin, London and his associates ¶ have demonstrated that in adults, at least 11% of the circulating bilirubin is derived from sources other than mature erythrocytes. They suggest as possible sources, marrow cells, catalase, myoglobin, peroxidase, and the cytochromes. To what extent these play a role in neonatal jaundice is not known.

In 1930, Rich[16] described neonatal icterus as a retention jaundice due to the inability of immature liver to excrete the bilirubin liberated by the destruction of the excess erythrocytes of fetal life. The fact that icterus neonatorum is especially common in premature infants was emphasized. Rich, furthermore, parenthetically underscored the observation that a normal liver is capable of excreting, without jaundice, far more bilirubin than it commonly receives.

In contrast to the above views, the pathogenesis of the jaundice of hemolytic disease is commonly ascribed to excessive hemolysis resulting from the action of the maternal Rh antibody upon the infant's Rh-positive red cells. This mechanism is important, but that it is the only, or even, necessarily, a significant, cause of hyperbilirubinemia in any given Rh-positive infant of a sensitized Rh-negative

‖ A personal communication from Dr. Weech revealed that this infant survived, with brain damage interpreted as a consequence of kernicterus.

¶ References 14 and 15.

mother, is decidedly questionable. If the pathogenesis were as simple as sketched above, the Rh antibody adsorbed upon the infant red cells (Coombs's test) should always be demonstrable. Furthermore, the intensity of this test should be very closely related with both the degree of hemolytic anemia and the degree of bilirubinemia. Actually, these correlations are sometimes completely absent or of such a low order as to prohibit definitive conclusions.

In 1947, Parsons [5] wrote that kernicterus of hemolytic disease was a result of liver damage and not of hemolysis. This conclusion was based upon the lack of correlation between the degree of hemolysis on the one hand and the severity of jaundice or the presence of kernicterus on the other. Vaughn and co-workers [17] wrote that the Coombs's test had not proved an accurate index of the severity of hemolytic disease and that in at least two cases of kernicterus with hemolytic disease, it had been repeatedly negative. The same group, in another paper,[16] wrote that the incidence of kernicterus was virtually independent of the degree of anemia and that, "there is no evidence in this series of tests that the strength of the reaction of the baby's washed cells with undiluted anti-human rabbit serum has any relation to the severity of the disease encountered." The authors reported seeing babies with strongly positive Coombs's tests who had no clinical disease, as well as, "a few infants in whom a negative Coombs's test was associated with fatal erythroblastosis fetalis (kernicterus)."

In hemolytic anemia of the newborn, the converse has been observed repeatedly, namely, a progressive but self-limiting anemia in Rh-positive infants of hypersensitized Rh-negative mothers, with the development of little or no jaundice.[18]

In the preceding short review of Weech's [13] and Rich's [16] monographs lies, at least in part, the explanation of these apparent parodoxes in hemolytic disease of the newborn. Approximately 50% of all infants develop physiological jaundice.[20] The hyperbilirubinemia reaches its peak between the second and fourth postnatal days, depending directly upon its initial height. This observation was made by Davidson, Merritt, and Weech, in 1941 (cited by Weech [13]), confirming with satistically significant data the work of Ylppö and Hirsch, in 1913 (cited by Weech [13]). It has been confirmed most recently by Mollison and Walker [21] and by Hsia and co-workers.# This is true of infants, regardless of the presence or absence of isoimmunization. Thus, in about one-half of all cases of hemolytic disease, there exists, in addition, the probability of physiologic jaundice. If one keeps in mind the fact that physiologic jaundice may occasionally be severe, it becomes evident that an Rh-positive infant of a sensitized Rh-negative mother may develop intense jaundice and even kernicterus without actually having hemolytic disease of the newborn. In contrast, the occurrence of hemolytic disease of the newborn without significant jaundice * may be interpreted as indicating that, in the presence of adequate liver function, jaundice need not develop.

Logic dictates the assumption that in hemolytic disease of the newborn, the more Rh antibodies adsorbed to the infant's red cells, the more severe the hemolysis and the greater the production of bilirubin. At this point, however, the chain of events leading to jaundice is interrupted by the liver. The degree of maturity of this organ determines to a large extent the presence or absence of neonatal jaundice in the

References 11 and 22.
* References 19 and 20.

premature infant, the term infant, or the infant with hemolytic disease. Thus, in hemolytic disease of the newborn, all degrees of correlation may exist between the Coombs's test, hemolytic anemia, and bilirubinemia without necessarily posing a paradox. On the whole, since the newborn liver tends, in the first postnatal days, to excrete bilirubin poorly, the more bilirubin produced, the greater the probability of developing marked jaundice. This is usually the case in hemolytic disease of the newborn. The more immature the liver, as in prematurity, the more intense is the jaundice, even without undue hemolysis,[24] and the more severe its complications. It is evident that the most unfavorable course will be followed by the premature infant with hemolytic disease. This has proved to be the case.[20]

Grundorfer's [23] interesting cases of "latent hemolytic disease of the newborn infant" are illustrative of those described by others.[25] Certain Rh-positive children with 4 + direct Coombs's reactions, born of sensitized Rh-negative mothers, show no evidence of hemolysis until several days to weeks after birth, when the striking pallor of the child is noted and the hemolytic anemia recognized. These children characteristically develop no jaundice, regardless of the degree of blood destruction. The reason for the apparently delayed hemolysis is not known, but the absence of jaundice probably attests to the ability of the matured liver to excrete unusually large amounts of bilirubin without a significant rise in the serum level. A case [26] of congenital spherocytosis (acholuric jaundice) in a newborn infant illustrates admirably the ability of the matured liver to handle very large amounts of bilirubin without the production of jaundice. On the 10th postnatal day, the child's hemoglobin was 18.3 gm. per 100 cc. and the red cell count, 6,900,000 per cubic millimeter. The infant was discharged on the 14th day as perfectly well, only to return three days later with a hemoglobin of 7.1 gm. per 100 cc. and a red cell count of 1,890,000 per cubic millimeter. The infant was pale, but not jaundiced.

It is firmly held [18] that at birth both physiologic and erythroblastotic jaundice are usually absent. They develop hours to days after birth. Weech [13] demonstrated that even with serum bilirubin levels above 12 mg. per 100 cc., occasional newborn infants do not develop jaundice and that a "critical level of serum bilirubin, above which icterus is present and below which it is absent, does not exist." Anselmino and Hoffmann [27] demonstrated in nonicteric normal newborn infants that the iontophoretic application of histamine resulted in the appearance of a jaundiced wheal. It appears, therefore, that for some reason the skin of the newborn does not stain as readily with bile pigment as it does shortly thereafter.

Case 4 of the present series, despite a survival period of seven days, had icterus of the aortic intima and kernicterus, but was not externally jaundiced. Two other patients, Cases 1 and 6, showed only mild cutaneous jaundice. This is of some significance in view of what has been written above and of Zuelzer's statement [28]:

> Several of the patients did not have clinical jaundice at any time, and even at autopsy none of the other organs was visibly jaundiced. That is not to say they did not have hyperbilirubinemia. The majority were icteric, but in the majority of the infants of group 2 (non-erythroblastotic kernicteric children) the icterus was not greater than that ordinarily classified as physiological jaundice, especially in a premature infant.

The hiatus between the serum bilirubin level and the intensity of cutaneous jaundice in the newborn infant, particularly the premature infant, may be much greater than has been suspected. Furthermore, in some newborn infants, the

impervious quality of the skin to the bilirubin may persist longer than the high liver bilirubin threshold. Thus, despite the presence of unusually high bilirubin serum levels, cutaneous jaundice may be mild or entirely absent.

Kernicterus.—In respect to the pathogenesis of kernicterus, many theories have been elaborated.† Some are projected back from experience with the adult brain and from experimental data suggesting that the basal nuclei are initially injured by hypoxemia, either through birth trauma, apnea, severe anemia, vascular occlusion, or unknown mechanisms. Another thesis advances the possibility that the brain injury is due to a antigen-antibody reaction. Regardless of the exact mechanism hypothesized, all theories are uniform in suggesting that the nervous tissue is first, seriously injured and second, stained.

Alternately, it has been hypothesized that bilirubin or its products are the primary injurious agents. None of the advocates of this theory have specified the nature of the process until quite recently, when Najjar [30] advanced the interesting suggestion as follows:

> Bilirubin is a molecule that is similar to heme in shape and structure even through it is not a completely closed ring and lacks iron. In this sense, it can be considered as an analogue of heme and, therefore, can compete with it at the active surface of the heme containing enzymes, such as the cytochromes. This interference in the function of the cytochrome system, when large concentrations of bilirubin are present in blood and tissue, may be sufficiently great to produce damage to the respiratory activity of the brain, a tissue which is particularly sensitive to derangement of the respiratory processes. The fact that the early newborn period is the most favorable time for the development of kernicterus may be related to the greater permeability of this young tissue to bilirubin.

Two of the concepts of the causation of kernicterus may be discarded. There has been no histologic evidence or experimental confirmation that vascular occlusion plays a role in kernicterus.[31] Nor has evidence in support of the etiology of the antigen-antibody reaction been reported, other than the occurrence of kernicterus in hemolytic disease of the newborn.

The possibility that anemia, especially in hemolytic disease of the newborn, may be a significant factor in the genesis of kernicterus is effectively denied by almost all who have inquired into this possibility. Thus, for example, Claireaux [29] observed that among his kernicteric babies the hemoglobin concentration ranged from 70 to 120% (Sahli). Day and Perry [31] stated that there was little or no correlation between the degree of anemia and the occurrence of kernicterus. Very significantly, Pickles [25] pointed out that in the most anemic newborn and stillborn infants with hemolytic disease of the newborn, the hydropic babies, there was neither jaundice nor kernicterus.

Birth trauma may result in severe hypoxemia, with permanent brain damage. The greatest hazard in this respect is to the firstborn. Craig [32] and Asher and Schonell,[33] in their studies of birth trauma, found that the percentage of firstborn children among their patients was 75 and 56.4%, respectively. In contrast to this, the vast majority of all children with hemolytic disease are preceded by at least one sibling. Among the 11 infants without hemolytic disease in the present report, none were firstborn and 9 were preceded by full-term siblings.

† References 25 and 29.

Among the 368 patients of Asher and Schonell,[33] there were 55 "athetoids." Nineteen of these were known to have had severe hemolytic disease of the newborn, and were believed to be survivors of kernicterus. Of the remaining 36 "athetoids," 12 gave a history of severe neonatal jaundice without evidence of hemolytic disease. Among the 313 other nonathetoid cases of birth trauma, only 7 had a history of neonatal jaundice. The authors were led by these data to make the following statement:

> This suggests that neurological complications of icterus neonatorum are not peculiar to cases of Rh incompatibility and cannot therefore be the result of antibody fixation in the tissues. The jaundice itself, or the hepatic insufficiency of which it is the sign, appears to cause the nuclear damage which results in athetosis.

This material is the only evidence encountered that the late neurological sequelae of kernicterus without hemolytic disease may be identical with those of hemolytic disease.

In regard to the theory of the anoxic causation of kernicterus, it is of interest to note, if we may draw an analogy from experimental work, that the very infants who supposedly show the greatest evidence of such damage, the premature infants without hemolytic disease, belong to the group of infants probably most resistant to such injury. In animal experiments,[20] it has been demonstrated that newborn mice, rats, rabbits, and dogs are capable of surviving anoxia for periods fortyfold greater than those fatal to adults of the same species. This ability to survive anoxia is quickly lost, so that, for example, by the 10th to the 16th postnatal day, newborn rats have achieved parity with adults. Hicks[34] detected "virtually no damage or rarely damaged cortical neurons" in the brains of his newborn rats after exposure up to 50 minutes in a nitrogen atmosphere containing 0.03% oxygen. His description of the effects of this atmosphere were as follows:

> When immersed in nitrogen the newborn animal continued to breathe regularly for a few moments, then gasped and struggled irregularly for a minute or two, urinated and turned cyanotic. From the onset of cyanosis, it remained motionless except for a gasp every few minutes. If jostled, it gasped and moved its limbs briefly. The heart rate during asphyxia was slower than normal. . . .

When Hicks prepared the animals with iodoacetate, the anaerobic survival was reduced to about three minutes, which is characteristic of adult behavior in nitrogen.

In man, the maximum anaerobic survival time of the newborn consistent with little or no detectable cerebral damage is unknown. It is well known, however, that the newly born infant shows a remarkable resistance to anoxia. This is believed to be due to the persistence, as in the rat, from the fetal into the neonatal period of a relatively more anaerobic carbohydrate metabolism than exists in the postnewborn period. The administration to human newborn infants of iodoacetate eliminates the pyruvic acid excretion characteristic of anaerobic carbohydrate metabolism.[20]

Among the animal groups, the greater the prematurity, the greater is the resistance to anoxia. If this relation should be true of man, it seems improbable that anoxia, in the absence of other injury, would damage the brain of the premature infant more readily and frequently than that of the mature infant.

The presumed sequence of severe anoxia or other brain injury followed by staining of damaged neurons received support from at least two experiments. Day[35] produced kernicterus by injuring one of the cerebral lobes of rats with roentgen radiation. Jaundice was then produced by the occlusion of the common bile

duct and intravenous injections of bilirubin. The most recent similar experiment was reported by Vogel,[36] who injected bilirubin into the umbilical veins of rat fetuses. Kernicterus developed in the younger animals, following partial occlusion of the umbilical circulation for periods of 30 to 40 minutes. Kernicterus could not be obtained without impairment of circulation.

Such experiments indicate that if brain tissue is sufficiently damaged, it will be stained by circulating bilirubin, probably in much the same manner that intravascular trypan blue will localize in a cutaneous area of inflammation [37] or as a histamine wheal will selectively accumulate bile pigment in subicteric states.[27] These experiments only partially illuminate the problem of kernicterus. It is reasonable to credit the proposition that severe hypoxemia will aid in the production of kernicterus, but there is no good evidence that, in man, it is a necessary precursor. Indirectly, severe hypoxemia may contribute to the production of kernicterus through the impairment of liver function and the elevation of the serum bilirubin level. This mechanism may be extremely significant in prematurity, where periods of apnea and cyanosis are not uncommon.

Other experiments, much more physiologic than the preceding, are not so uniformly successful. Perhaps the first experimental kernicterus, a by-product of investigations on the hematoencephalic barrier, was produced by Froehlich and Mirsky,[38] who injected bile intraperitoneally into newborn rats. Up to the 10th postnatal day, the bile elicited severe protracted convulsions, and, in some animals, there was pigmentation of Ammon's horn. Beyond the 10th day, the bile was ineffective. Whether the convulsions may have resulted in severe apnea and cerebral hypoxemia was not discussed.

Experiments designed to simulate hemolytic disease of the newborn of man are exemplified by those of Eyquem.[39] Dogs and cats from 2 to 4 months of age were given graded doses of heteroimmune (rabbit) antiglobulin. In the largest dose group, severe hemolysis appeared and was accompanied by hemoglobinemia, hemoglobinuria, and intense shock and dehydration. The animals died by the fourth postinjection day, with icterus gravis; some proved to have kernicterus. The author stated his belief that the best explanation of the kernicterus lay in presuming the fixation of antibodies on the brain cells, with resultant necrosis and staining. Eyquem's use of a nonspecific antiglobulin to produce hemolysis is a severe restriction when comparing his lesions to those resulting from specific hemolysin. Dereymaker [40] reported similar findings in rats and dogs, utilizing the same approach. Day and Perry [31] could not confirm Dereymaker's findings. Young and co-workers [41] suckled pups with Type A antigen erythrocytes to dams secreting A antibodies in their milk. Despite severe hemolysis, neither jaundice nor kernicterus could be produced. They suggested that the bilirubin-excreting power of the newborn dog liver is too great to permit more than mild hyperbilirubinemia. In respect to the brain they stated, "Autopsy revealed . . . questionable evidence of specific injury of the nerve cells of the basal nuclei of the brain."

It is evident that the experimental approach to the problem of kernicterus leaves much to be desired. It is significant, however, that there is no clear-cut and confirmed evidence of injury to the basal nuclei in the absence of severe jaundice, without which the thesis of injury preceding bile staining cannot be sustained.

Each hypothesis in explanation of the genesis of kernicterus ‡ has its merits. However, it would appear that several well-documented observations must be adequately explained before any one proposal may be considered correct. These are as follows:

1. Kernicterus does not develop before birth.
2. Kernicterus does not develop after the first few neonatal days.
3. Premature and some term children without hemolytic disease of the newborn may develop kernicterus.
4. Exchange transfusions have effectively reduced the incidence of kernicterus in hemolytic disease of the newborn.

If kernicterus is the result of a mass action effect of the bilirubin, obviously kernicterus cannot occur when the bilirubin blood level is low. All studies of cord blood bilirubin levels § show that it rarely rises above 10 mg. per 100 cc. There is evidence, although inconclusive, that this limitation is due to placental excretion of bilirubin.[24] Since kernicterus is most apt to occur when the bilirubin rises above 30 mg. per 100 cc. and is unlikely to occur if it remains below 20 mg. per 100 cc.,‖ it is apparent that kernicterus will not occur in utero.

Considering the second observation, that kernicterus does not develop after the first few neonatal days, it must be recorded that Rutledge and Neubuerger [42] did report, in a 74-year-old woman with severe obstructive jaundice, bile-staining of an encephalomalacic area. Nonetheless, in man, kernicterus, as it occurs in the newborn, has never been described as developing in the postnewborn period.

It would appear that the common finding of kernicterus in the premature infant and in the infant with hemolytic disease must depend upon some factor or factors characteristic of the neonatal period.

As already mentioned, Froehlich and Mirsky,[38] in 1942, demonstrated a definite correlation between age and susceptibility of the brain to the effects of bile. This was also true of acid fuchsin. The pretreatment of animals with theophylline, which increases the permeability of isolated blood vessels, increased the susceptibility to acid fuchsin. Similar pretreatment with vitamin D [43] protected young rats from the convulsant effects of both acid fuchsin and bile. The author [43] concluded that "these findings are consistent with the hypothesis of the development of a functional type of hematoencephalic barrier in older animals which controls the transfer of some agents from blood to brain." Vogel's work [36] led him to the conclusion that, "prematurity and anoxia may alter the blood-brain barrier so that bilirubin, when present in excess, in the blood, may pass into the cerebral tissues . . . ."

Bile giving the indirect van den Bergh reaction is uniformly demonstrable in the spinal fluid of all newborns.[44] While its absolute concentration was not determined, it was found to fluctuate directly with the serum bilirubin in a proportion of about 1 : 125. In adults, information on spinal fluid bilirubin in icteric states is incomplete and, in part, contradictory.¶ The most authoritative statement [48] indicates that, while in adults, "no correlation between amount of bilirubin in fluid and degree of hyperbilirubinemia" existed, among 21 jaundiced persons, 20 showed

‡ References 25 and 29.

§ References 11, 13, 22, and 24.

‖ References 11 and 22.

¶ References 45-47.

bile in the spinal fluid. Several of the patients had hepatitis; the majority had portal cirrhosis. The bilirubin was invariably of the prompt-reacting type. Studies on the correlation of spinal fluid bilirubin levels with bilirubinemia in purely hemolytic states could not be found in the literature available to us. Since data concerning the concentration of spinal fluid bilirubin in kernicteric babies is lacking, the importance of the degree of permeability of the hemoencephalic barrier in the causation of kernicterus cannot be properly evaluated. From the occurrence of kernicterus only during the first days of the neonatal period, however, and from experimental data typified by that of Froehlich and Mirsky,[38] it would appear very probable that the increased permeability of the barrier during this period, subject to individual variations, is one of the principal limiting temporal factors in the pathogenesis of the lesion.

Concerning the third observation, that premature and some term infants develop kernicterus without the mediation of undue hemolysis, it may again be pointed out that in the infant with hemolytic disease there exists a high correlation between the intensity of the bilirubinemia and kernicterus.# In addition, it has been demonstrated [21] that the birth serum bilirubin levels of premature infants without hemolytic disease parallel those in hemolytic disease.

That hyperbilirubinemia is, of itself, associated with kernicterus is demonstrated by the case of Crigler and Najjar,[8] who discovered within a family group an inherited bilirubin excretion defect of the liver. Among the children of this family, one case of kernicterus was demonstrated and a number of those affected developed the neurologic signs characteristic of kernicterus. All members of the family were Rh positive and isoimmunization could not be demonstrated.

Examination of Table 1 reveals that 8 of our 13 infants were, by weight, premature, each weighing 2,000 gm. or less.* Of the remainder, three were immature and only two were mature term children. Zuelzer and Mudgett [1] reported a 25% prematurity among their kernicteric infants without hemolytic disease. Aidin, Corner, and Tovey [2] had 23 premature and only 1 mature infant in their group. Ahvenainen and Nevanlinna [9] noted among 28 similar icteric infants that 18 were premature and 10, mature.

It is pertinent to the discussion to recall the previously cited case of Weech, that is, a full-term infant who developed severe "physiological jaundice," with a serum bilirubin level of 40 mg. per 100 cc. The child was Rh compatible with its mother and was never anemic. There was no demonstrable ABO incompatibility. The infant developed the neurologic signs of kernicterus and was permanently crippled. This case indicates the heights which bilirubin may occasionally reach without the added hemolysis of isoimmunization. Full-term mature children without hemolytic disease of the various series with kernicterus may be analogous to this instance.

The reduction in the number of kernicteric babies resulting from exchange transfusions in hemolytic disease of the newborn [21] can only be explained by a mechanism which precludes severe brain injury preceding the bile staining of the nuclear masses. Obviously, if the brain were severely injured prior to staining, this injury should persist despite exchange transfusion, and the incidence of dead

References 4 and 21.

* The range and median of Japanese birth weights seem to be identical with those of Occidental infants.

and neurologically damaged babies would remain unaffected. The effective reduction in the morbidity and fatality rate of kernicterus is a powerful negation of the "preceding anoxia" school of thought.

Thus it would appear that kernicterus occurs in the newborn group with the greatest bilirubinemia. Among full-term infants, it is most often a complication of the jaundice associated with hemolytic disease of the newborn. Among the premature infants, it is most commonly a complication of "physiologic jaundice." The latter group constitutes a clear-cut majority of all cases of kernicterus. In addition, the presence of any lesion tending to reduce the level of liver function, for example, pneumonia, might well contribute to a further rise of serum bilirubin, increasing the possibility of kernicterus without any known or demonstrable direct effect upon the brain. Such lesions or states were not noted in our cases.

Pigment of Kernicterus.—The nature of the pigment in kernicterus is not yet firmly established.† The working assumption has been that it is bilirubin or a derivative. The most recent information on this subject is a study on the nature and deposition of kernicterus pigment.[36] Extraction of the kernicterus pigment from three infant brains gave a diazopositive material which electrophotometrically showed the characteristics of crystalline mesobilirubin. The injection of billirubin into the umbilical veins of living rat fetuses, the flow of placental blood having been diminished for a period of 30 to 40 minutes, resulted in pigmentation of the brains of the less mature animals. Since it had been demonstrated [49] that the brain, in vitro, may convert bilirubin to mesobilirubin, Vogel [36] concluded that kernicteric pigment is composed of mesobilirubin. It would have been of some interest had the author studied the nature of the pigment in his experimentally stained brains.

Other forms of bile pigment have been suggested.[25] Among the brains of our material, four gave positive and three, negative Gmelin reactions. Of the four positive brains, two were very clear-cut, and two were less so but, nonetheless, showed a color change to nitric acid application. This small series indicates that at least in some brains with kernicterus, the pigment, or an appreciable part of it, is bilirubin.

Liver.—Hsia and co-workers [50] have most recently investigated the syndrome of prolonged obstructive jaundice in infants. Of 156 such patients, 23 (15%) had associated hemolytic disease of the newborn; in 30 (19%) the etiology was unknown. Not pertinent to the present study were 94 (60%) instances of bile-duct atresia and 9 (6%) with other causes of jaundice. The two groups of 23 and 30 cases were believed to have the syndrome of "inspissated bile" as the basis for the biliary obstruction. Twenty of the second group were operated upon and liver biopsy specimens examined. The operations were undertaken in the hope of repairing the presumed bile-duct obstructions. In 16, the ducts were normal, in 4, they were thought to be small and stenotic, although not atretic. The livers revealed marked plugging of bile capillaries by bile thrombi. All the children with hemolytic disease and about 60% of the group without known etiology were later spontaneously relieved of their jaundice. The authors, discussing pathogenesis, suggest, among other possibilities, a decreased bilirubin excretion as a result of liver immaturity. Additional factors in the case of the infants with hemolytic disease were the overloading of the liver with bilirubin and in the others, dehydration. Among the

† References 24 and 25.

30 infants without hemolytic disease of this series, 9 were premature and several others had low birth weights. It would appear reasonable to suggest that some, if not all, might have been instances of severe "physiologic" jaundice.

SUMMARY

Definite evidence of the central nervous system toxicity of bilirubin or some related compound in man has not yet been reported, but the preceding data appear to support such an assumption.

Thirteen cases of kernicterus without hemolytic disease were recorded among the dead newborn infants of a Japanese community. These cases, in every way, are comparable to those described in the Occident. Occurring among a people whose Rh-negative members constitute only 0.44% of the total population, they confirm the conclusion that physiologic jaundice is responsible for more cases of kenicterus than is hemolytic disease of the newborn.

Both physiologic jaundice and hemolytic disease of the newborn are examples of retention jaundice characterized by an increase of indirect bilirubin. The jaundice is due to the inability of the immature neonatal liver to excrete, in the former syndrome, the normal load of bilirubin, and, in the latter, bilirubin of the same source and quantity plus that contributed by the hemolytic system.

Premature infants, and some full-term children with greater hepatic immaturity than usual, develop bilirubinemia levels comparable to those of hemolytic disease. Several sequelae may occur, namely, kernicterus, probably the syndrome of "inspissated bile," and chronic obstructive jaundice.

Kernicterus is probably a result of the increased permeability to bilirubin of the hematoencephalic barrier of the neonatal state. The bilirubin may possibly, by mass action, replace one or more vital substances which may damage or kill the involved cells.

While severe hypoxemia or periods of anoxia may promote directly or, more probably, indirectly the production of kernicterus, it is doubtful if they are a necessary precursor of the lesion.

There is indirect evidence in the literature that the late manifestations of kernicterus of physiologic jaundice may be identical to those of kernicterus with hemolytic disease.

The recognition of two components in some instances of jaundice with hemolytic disease, physiologic jaundice and a specific hemolytic jaundice, as well as the realization of the potential gravity of physiologic jaundice, makes it possible to explain several of the apparent inconsistencies described in hemolytic disease of the newborn.

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APHASIAS IN CHILDREN

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APHASIA is a very complex problem. It has been studied by neurologists, physiologists, psychologists, and speech clinicians. Because of the diverse approaches used by the investigators, aphasia has been a subject of great controversy. In recent years, however, it has become evident that, whichever approach interests the investigator, he must take account of the others.

A good definition of aphasia is given by Fulton [1] in Howell's textbook on physiology, "The term aphasia means literally the loss of the power of speech, but the term is now used to include any marked interference with the ability either to use or to comprehend symbolic expression of ideas by spoken or written words or by gestures, or interferences with the use of language in thinking."

To be really exact, we should differentiate between speech and language. Language is a psychic process centered in the cortex and in its widest sense signifies the expression of thoughts and ideas. The sign language used by the American Indians and the early settlers, the manual communication of deaf mutes, or the language of the eye is language just as much as verbal communication. At best, however, the sign language has only a very limited field of usefulness. It can express only limited ideas and simple primitive emotions, such as pleasure, anger, and surprise. It is only with the development of speech that we are able to express subtle ideas and thoughts both concrete and abstract.

Speech is the symbolic expression of feelings, thoughts, and ideas through words. It is the verbal means of communication and may be regarded as both a tool and a manifestation of language.

In general usage, however, the terms speech and language are used interchangeably, and in this presentation these terms will be so used.

In aphasia we are dealing with a disturbance of function of certain areas in the brain concerned with speech and language.

There are still differences of opinion as to the specificity of function of certain areas of the brain. If placed on a continuum, one end of the scale would represent an attitude of pinpoint specificity of function, localized in circumscribed areas, so-called centers, while the opposite extremity would represent an attitude of almost complete equality of function in all parts of the cortex, the nonlocalization viewpoint. The consensus today is that there is specialization of function of certain areas of the brain but at the same time there must be an over-all integration of the cortex in control of function.

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Penfield and Rasmussen,[2] in the course of operative procedures on patients under local anesthesia, carried out electric stimulation of various regions of the brain. Vocalization and speech arrest resulted from stimulation of the superior frontal and Rolandic areas. Electric stimulation of either of these areas, in either hemisphere, produced, at times, an isolated response of vocalization—a cry without words —but more commonly the response was to stop speech, interrupt counting, or slow down the speaking.

Aphasic arrest resulted from stimulation of frontal, parietal, and temporal areas of the dominant hemisphere. Here the patient knew what he wanted to say but could not say it. He might say, "that is a —," then stop, unable to remember the

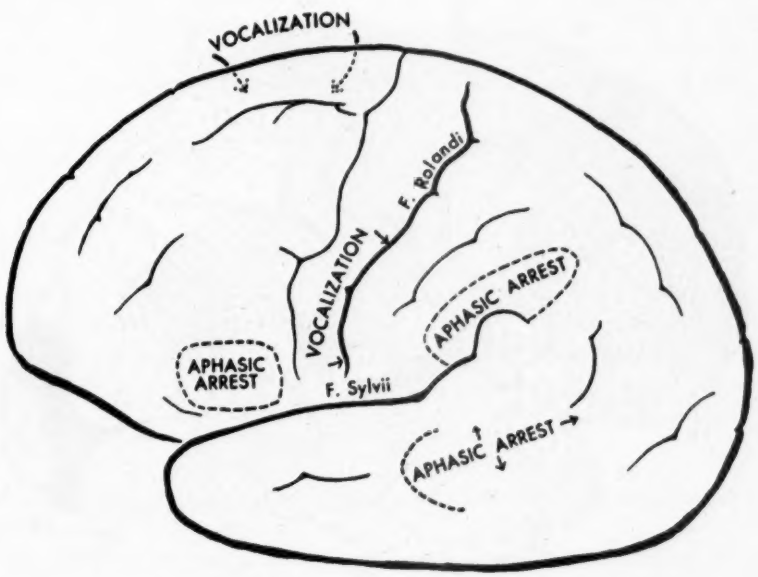

Fig. 1.—Areas of vocalization and of aphasic interference with speech. The vocalization area in the rolandic cortex and that within the longitudinal fissure are found in both hemispheres. The three areas—frontal, parietal, and temporal—in which stimulation produces temporary aphasia are marked "aphasic arrest." They are found only in the dominant hemisphere (from Penfield and Rasmussen [2]).

name of object shown to him, or he would become confused and use words wrongly, just as an aphasic would do (Fig. 1).

In no case was aphasic arrest produced when the vocalization and speech arrest areas were stimulated.

These experiments would seem to indicate that the arrest of speech and language function is associated with specific brain areas and that aphasic arrest is found only in the dominant hemisphere.

The normal activity of the central nervous system depends upon the interaction of two systems, the sensory and the motor. The sensory, or receptive, component of speech consists of comprehending spoken or written language, i. e., spoken words

or written symbols. The motor or expressive component of speech consists in the ability to express words or written symbols. In the development of speech, associations are formed between verbal sounds or words and meaning. At the same time, pathways are elaborated and utilized. These associations and associative connections are established in specialized parts of the brain.

The auditory area in the superior temporal gyrus is Area 41; it also occupies the floor of the Sylvian fissure and is surrounded by the psychoauditory zone, Area 42. Area 37, which is immediately anterior to the occipital lobe, is the language-formulation area, where the child lays down engrams for the proper arrangement of

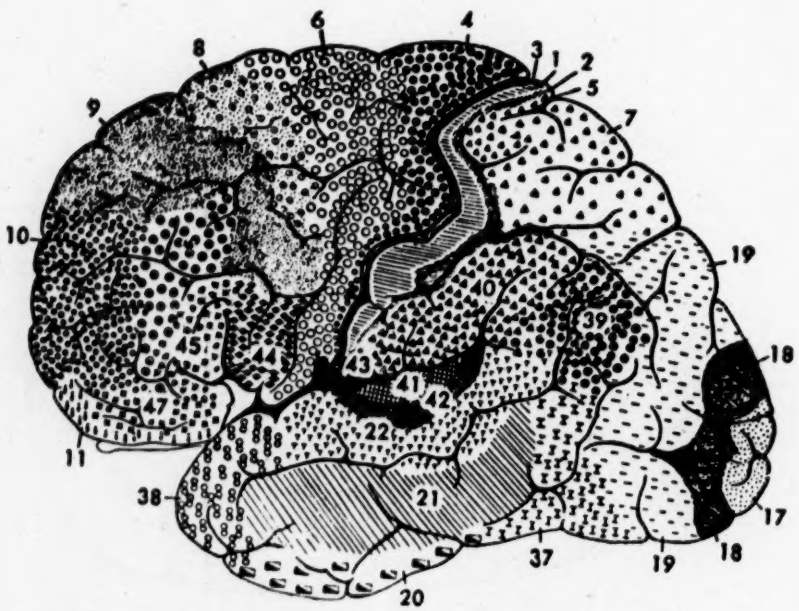

Fig. 2.—Cytoarchitectonic fields of the human cerebral cortex (from Brodman [1909]).

words into sentences. The visual cortex surrounding the calcarine fissure is Area 17. The visual word area is in the angular gyrus, Area 39.

The motor, or expressive, area is located at the posterior end of the inferior frontal convolution, Area 44, and is known as Broca's convolution. Broca's area is not the direct cortical representation of the muscles of speech, but it lies just anterior to it. The writing area is part of the cheirokinesthetic area and is situated above Broca's area (Fig. 2).

It is evident from these observations that the receptive areas for speech are situated in the posterior part of the cortex, while the motor areas are primarily associated with the anterior part of the cortex. It is also evident that the area of the cortex devoted to the reception of speech is much larger than that occupied with its expression.

Another distinctive attribute of the human brain is the dominance of one cerebral hemisphere over the other in the performance of language function. This is related to handedness, since in most right-handed adults the speech areas are situated in the left cerebral hemisphere, which is the dominant, or major, hemisphere. The evidence for this is that a right hemiplegia is usually accompanied by a language disorder, but this is not true for left hemiplegias.

It is justifiable to assume that directly after birth and until the end of the first year the two hemispheres act together in all performances and a functional differentiation between the two hemispheres does not exist. Goldstein [3] states that at this age stimulation of the motor area of each hemisphere is followed by twitching movements in both sides of the body. The infant uses both hands randomly. As the infant grows older, handedness begins to appear. Gesell [4] states that laterality is distinctly a morphological phenomenon, that it represents a form of dynamic asymmetry. McCarthy,[4] in her studies of language development, observed that lateral dominance apparently becomes established toward the end of the first year

Per Cent of Children in Whom Handedness Is Established in Relation to Intelligence Quotient

I. Q. Range	C. A. *	M. A. †	Handedness Established
15-25	3 yr. 9 mo. to 14 yr. 0 mo.	0 yr. 6 mo. to 3 yr. 9 mo.	50%
26-50	3 yr. 0 mo. to 13 yr. 7 mo.	1 yr. 3 mo. to 6 yr. 0 mo.	65%
51-70	3 yr. 9 mo. to 14 yr. 1 mo.	1 yr. 8 mo. to 7 yr. 11 mo.	92%

* Chronological Age.
† Mental Age.

of life and during the first months of the second year, which is just the period when speech begins to emerge from the infant's early babbling.

We see, therefore, that as the child grows older there is a simultaneous development of higher mental functions, cerebral dominance, handedness, and language function. It would appear that these are all interrelated.

In a recent study that I made,[5] it was shown that there is a relationship between cortical development, language development, and the establishment of handedness.

This study was made on a group of 50 mentally deficient noninstitutionalized children who came to the Jewish Hospital Clinic for Retarded Children for guidance and diagnosis. The I. Q. of the children ranged from 15 to 70. The children were divided into three groups according to their intelligence quotient as established by the Stanford-Binet, Form L, and the Kuhlman tests of mental development, individual form. The chronological age of the children in each group was approximately the same. The mental age of each group, of course, was different.

Next, the established handedness of the children in each group was determined. The conclusions were based on the parents' statements and on our own direct observations at the clinic. The child's hand preference, strength, and coordination in the performance of simple tasks were noted.

The findings were that the group with the higher I. Q. had a greater percentage of established handedness. The figures were also subjected to a statistical analysis, and the results were found to be statistically significant. It was also noted that the children with higher I. Q.'s had better language ability (Table).

The results of this study indicate that a positive correlation exists between the degree of brain development and the development of language and handedness.

Aphasias in children may be either (1) receptive—where the child is unable to understand spoken or written language, or (2) expressive—where the child understands but is unable to use meaningful language.

Clinically, the aphasic child presents varying degrees of both forms of defect in language function, receptive and expressive, and it is perhaps best to speak of a certain case as being predominantly receptive or predominantly expressive.

Aphasia in children is a controversial topic. Some deny the existence of congenital aphasia unless there is severe bilateral brain damage. Some object to the use of the term aphasia in children who never developed speech, since aphasia implies the loss of a previously existing function, and to some, aphasia in children implies an unusual congenital language disorder.

While theoretically one may postulate that congenital aphasia does not exist as an entity, clinically there is no doubt that there are children with severe language disabilities who are misdiagnosed as cases of deafness, emotional disorder, or mental retardation. Cognizant of the fact that there are differences between aphasia in the adult and aphasia in the child, for semantic reasons, I believe, aphasia is a good generic term, since it denotes a cerebral form of language dysfunction. Finally, the term aphasia in children should not only imply a congenital disorder, for aphasia in children may have different etiologies. I propose the following classification.

Aphasias in Children

A. Acquired
   1. Acute—due to
      infections
      convulsions
      migraine
   2. Subacute—due to
      tumor
      abscess
   3. Chronic—due to
      hemorrhage
      injury

B. Congenital
   1. Speech aphasias
      (a). Word deafness
      (b) Dysphasia
   2. Visual aphasias
      (*a*) Alexia, or word blindness
      (*b*) Agraphia

The acquired aphasias have the following in common: 1. They are secondary to some definite pathology in the brain; the result of infection, tumor, or cerebral vascular accident. 2. They all present neurological signs or have laboratory evidence of brain pathology.

In congenital aphasia we are dealing with a child who presents a failure in the development of language function without any history or neurological signs of brain injury or disease.

We must bear in mind that it is the site or location of the involvement in the brain rather than the pathological nature of the lesion that determines the symptom complex of aphasia. After the presentation of some case material to illustrate the acquired aphasias, I shall return to the discussion of the congenital aphasias.

ACQUIRED APHASIAS

I. The following case illustrates the acute type of acquired aphasia.

On August 16, 1952, at 3 p. m., a 12-year-old boy was admitted to the Jewish Hospital, Pediatric Department, service of Dr. Benjamin Kramer.

The child, who had been well, shortly after waking in the morning complained of a mild left frontal headache. He ate breakfast and shortly after complained of a severe nonthrobbing left frontal headache and vomited. He continued to vomit for about 15 minutes, and then his mother noticed that the boy could not talk. A physician was called, and the child was admitted to the hospital.

In the hospital admitting room, the boy vomited twice. At this time (3 p. m.) he was hyperactive, thrashing about, and uncooperative. He made many attempts to talk and to answer questions, but was able to say only one or two words. He could not complete the thought and was completely incomprehensible He was unable to give his name.

The following day he was no longer restless and lay quietly in his bed (T. 99 F., P. 100, R. 22). His speech improved somewhat, but frequently he would get "stuck" on words. It was evident he knew the thought behind the words, since he would try to use a word with the same meaning. He could not name a pencil or key but would say "what you write with," "what you open a door with." He was able at this time to write out his name, age, and address, but had impaired calculating ability.

During his 10 days of hospitalization, his spinal fluid was examined on three occasions. It was clear and contained between 170 and 70 cells per cubic millimeter, of which 90% to 100% were lymphocytes Protein was 36.4 mg. per 100 cc., sugar 86 mg. per 100 cc., and chlorides, 430 mg. per 100 cc. His blood revealed a HGB. of 16 gm. per 100 cc. and 5,000,000 red blood cells per cubic millimeter. The WBC was 16,500, with 90% polymorphonuclears; this later fell to 10,450, with 58% polymorphonuclears.

Neurological examination was essentially negative, except for some inequality of deep reflexes, right slightly more active than left.

His speech gradually improved, so that on the fourth or fifth day following admission it was practically normal. He told me, "It got me mad and scared because I could not talk. I knew what I wanted to say but I could not say it." The final diagnosis was acute encephalitis, with complete recovery. The boy had an aphasia predominantly expressive in type.

Transient aphasia may follow convulsions. The aphasia may last for a few days or disappear in a few hours.

Temporary aphasia may follow an attack of migraine.

II. The subacute types of aphasia are the language disturbances that the child may develop as a result of brain tumor or brain abscess.[6] The speech and language disturbances here are not as dramatic as in the previous type and are frequently overlooked.

Here we are dealing with a sick, apathetic, and morose child. Not much attention is paid to the speech and language disturbance. A child 6 to 7 years old may show complete mutism. An older child, 10 to 12 years of age, may show hesitancy in speech, distorted speech, a "telegram" style of speech, or the speech picture seen in adult aphasics.

Once the underlying pathology is removed, recovery from aphasia is good; most patients recover in about four weeks.

III. In the chronic type, the symptomatology resembles the aphasias seen in the adult and is usually the result of some cerebral vascular accident.

From this group I would exclude children with cerebral palsy, who present characteristic speech problems of their own.

This type of aphasia in a child may be illustrated by the following case observed at the Jewish Sanitarium and Hospital for Chronic Diseases, service of Dr. Abram Kanof.

A boy, 10 years old, had right hemiplegia and marked weakness of the right upper and lower extremities.

This was a high forceps delivery with cerebral hemorrhage. A decompression operation was done 24 hours later. The boy has a 2-in. (5 cm.) scar in the left temporoparietal region.

The boy understood signs and spoken language but did not communicate verbally, even in the simplest fashion. He used gestures to indicate his needs or wants. On the ward he was well behaved and cooperative He was anxious to help the nurses to take care of and feed the other children.

The general impression was that the boy was normal mentally.

The electroencephalogram on May 14, 1952, was reported as normal.

The psychologist reported that the boy comprehended direction on a concrete level, perseverated, was unable to concentrate, and had a short attention span. When unable to perform a task, he would keep on trying, then would become frustrated, have an outburst of temper, and throw the testing material on the floor or scatter it on the desk.

He gave no sign of speech and made sounds that can only be described as grunts. When he made these sounds, he appeared to be able to perform the physical movements necessary for speech.

My impression was that we were dealing here with a child who had sustained damage to the left cerebral hemisphere, resulting in aphasia predominantly expressive in type.

CONGENITAL APHASIAS

Unusual as the acquired aphasias are, congenital, or primary aphasia, presents a much more difficult and, one may say, a more nebulous problem.

Children may fail to develop language due to mental deficiency, deafness, or severe emotional disturbances (psychosis), but these children present special problems of their own, and they should not be considered aphasic.

I. The clinical features of congenital word deafness are as follows:

A. The child does not talk or has limited speech. This is always the initial and outstanding symptom. It is the child's speech that the parents are primarily concerned about when they bring the child to the physician. The child of 3 or 4 years of age may have no speech at all, or an older child of 6 years of age may have limited and distorted speech.

B. The child shows a tendency to shyness, seclusiveness, and social withdrawal.

C. The child is mentally normal.

D. Physical and neurological examination is usually negative.

E. There is a negative history of illness and injury.

F. The child's hearing is the crux of the problem.

At first, the parents are certain that the child is able to hear. As the child grows older, it becomes evident that he is deaf to speech, and yet he is able to hear sounds. It soon becomes evident that the limited speech which the child does acquire is through lip reading. In the classic textbook picture, the child has normal or adequate hearing when tested with the audiometer, but is unable to comprehend words by the auditory route. In some cases, psychogalvanic skin-resistance audiometry may have to be used to substantiate the diagnosis.

I reported such a case in 1950.[7] The following is a brief summary of the case, with some additional follow-up information.

This boy did not talk until 4 years of age, when he began to use single words. When seen at 5 years of age, he had limited speech. It was evident he lipread, yet his parents were certain he

heard sounds. He was unresponsive to the voice test, yet he was able to pick out an appropriate toy by hearing the sound without visual aid. A tentative diagnosis of congenital word deafness was made. Several audiometric tests, however, revealed a 98% hearing loss. The question was, how did he acquire limited speech? How was he able to pick out a toy by its sound?

He was referred to The Johns Hopkins Hospital for psychogalvanic skin-resistance audiometry. The report was that the boy heard sounds, but his difficulty was a central verbal defect in hearing.

In 1952, I learned that the parents had taken the boy to another hospital. Routine audiometric tests again revealed a 98% hearing loss. To rule out hysteria or some other psychogenic factors, narcosynthesis was tried with amobarbital (Amytal) sodium. There was no response. The boy had some speech therapy. He attends a private school with normal children, and his school progress is good.

Congenital word deafness has been described under various names as follows: (1) congenital or infantile aphasia, (2) psychic deafness, (3) central deafness, (4) congenital auditory imperception, (5) congenital verbal imperception, and (6) congenital verbal auditory agnosia.

A better understanding of this problem can be had if we realize that in the development of speech, granted a normal intellectual endowment, hearing and speech form a closely interrelated function.

The cochlear division of the auditory nerve arises from the cells of the ganglion of the cochlea, the spiral ganglion, and passes into the medulla. Reaching the lower border of the pons, the fibers divide, one portion going to the dorsal, the other to the lateral cochlear nucleus. The fibers arising from these nuclei later unite and ascend in the lateral lemniscus to the inferior colliculus of the midbrain. The tract is continued as the brachium of the inferior colliculus to the median geniculate body, which is the subcortical auditory center. Fibers arising from the median geniculate body form the auditory radiation and ascend in the posterior limb of the internal capsule to terminate in the temporal lobe of the cortex (Fig. 3).

The primary center, where the auditory impulse arrives, is in the transverse temporal gyrus of Heschl, lying in the floor of the lateral (Sylvian) fissure. These gyri are not visible in the intact brain because they are covered by the parietal operculum. This is the auditosensory area, or the site of primary perception. Here the fundamental auditory sensations, intensity, quality, and pitch, are appreciated.

The impulse then travels further to the adjacent superior temporal convolution, or Wernicke's area. This is the auditory-psychic area where there occur the analysis and the interpretation of auditory sensations and their integration into more complex perception. Here occurs the recognition of sounds in general and of language in particular.

We must also bear in mind that certain cortical functions often referred to as higher, or as occurring on a higher cortical level, are dependent upon a more complex integrative activity than the cortical functions which are referred to as lower, or as occurring on a lower cortical level.* The development of language function also follows an order of increasing cortical complexity.

The infant at first receives sensory impulses, such as sound or vision, and he develops perception or an awareness of the sensory stimulus. These impulses end in the cortex at the first level, or, as Orton [10] called it, the "arrival platform."

* References 8-9.

The child next develops recognition, which is a cortical function on the next higher level above that of perception. At this second level the child develops the ability to recognize various objects and symbols, and memory constellations are developed which are capable of recall.

Later on, at a still higher, or third, level, some of these functions are further refined and enter the field of symbolic formulation. Concepts are formed, and language is elaborated. These are sensory levels.

In the motor sphere there is a similar arrangement in order of increasing integrative complexity: 1. At the first level, there is the ability to contract striated muscles

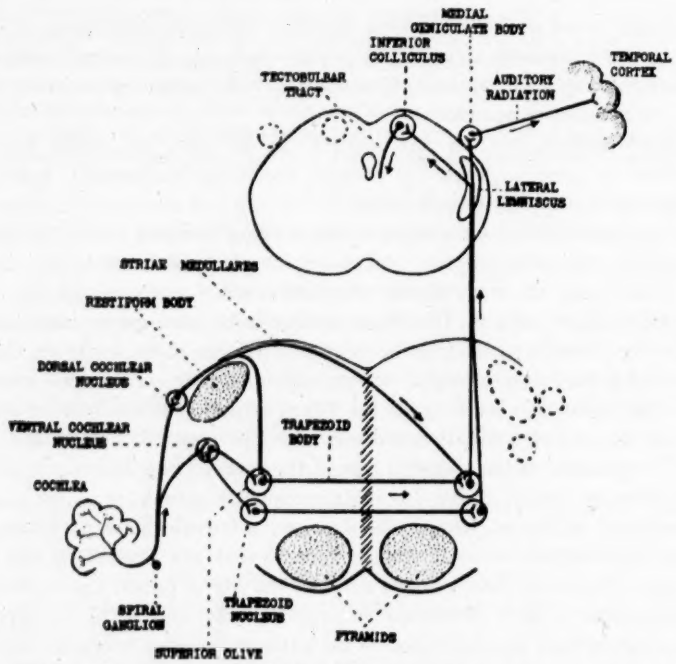

Fig. 3.—Diagram of the auditory pathway "The Physiological Basis of Medical Practice" (from C. H. Best and N. B. Taylor, [in part after Gray]).

voluntarily. 2. At the second level there is the ability to perform purposeful movements of varying degrees of complexity. 3. At the third level, there is the ability to express meaningful language (Fig. 4).

When there is a disturbance or disorder at any of these levels, the following will result:

On the sensory side—at the first level cortical blindness or deafness; at the second level, loss of recognition, agnosia, visual or auditory; at the third level, loss of concepts, aphasia.

On the motor side—at the first level, anarthria; at the second level, apraxia; at the third level, aphasia (Fig. 5).

Fulton [1] speaks of levels of language function. At the low level, receptive aphasia merges with agnosia, expressive aphasia merges with apraxia; at high levels, aphasia is probably the manifestation in the sphere of language of intellectual defects of a more general character.

II. Developmental motor aphasia or dysphasia is a more infrequent disorder. These children do not speak at all or make only primitive sounds. They demonstrate

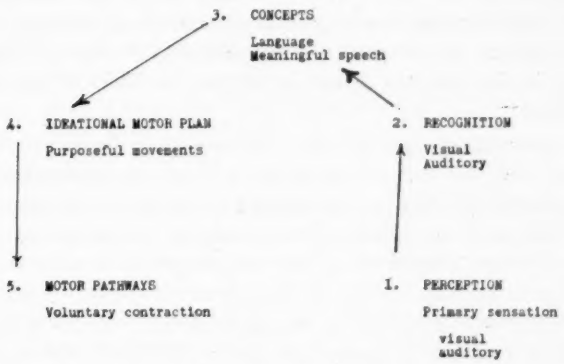

Fig. 4.—Diagram showing the developmental levels of cortical function.

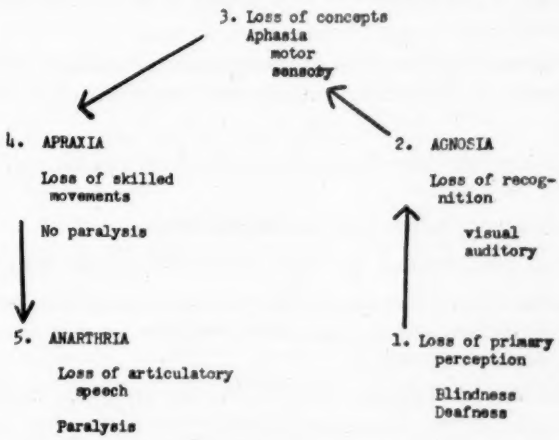

Fig. 5.—Diagram showing the disturbances produced at various levels of cortical function.

some understanding of speech and do not exhibit the auditory inattention characteristic of children with sensory aphasia.[11]

III. Congenital word blindness is a term applied to children who have an inability in learning to read. This defect is much more common than congenital word deafness and is more easily recognized, since the child is unable to read.

While there are various factors that may play a role in reading retardation,[12] there are some children whose reading disability is due to a congenital lack of the ability to appreciate the significance of visual symbols, developmental alexia.

Orton [10] demonstrated that many children suffering from developmental alexia exhibit mirror-writing tendencies, which may be secondary to mirror reading—"no" is pronounced as "on." He attributed this disorder to lack of development of cerebral dominance. Many of these children also have difficulty in spelling. Orton named this condition "strephosymbolia," which means "twisted symbols."

Bender [13] has shown that some of these children showed directional disturbances in the visual-motor gestalt function, a disorder in visual-motor organization.

Congenital word deafness, like congenital word blindness, is much more common in men than in women. The proportion is approximately five to one. These disorders are frequently familial and may appear in different members of successive generations of a family.

As to the pathogenesis, one can only speculate upon the underlying pathology. It may be assumed that the cerebral defect consists of incomplete development, or an aplasia of cortical regions concerned with the language function. It is possible that the theory I proposed,[14] that stuttering may be due to a delay in or lack of myelinization of cortical speech areas, may also be applied to these disorders.

Disturbances in language function is only one aspect of congenital aphasia. These children usually present, in a varying degree, behavioral changes in the intellectual and emotional field, as well as marked changes in the general personality make-up:

1. There is a tendency to social withdrawal, shyness, and seclusiveness: The child reacts more or less normally to those stimuli in his surroundings which he is able to understand.

2. The child may show, at times, aggressiveness and irritation. He may "fly off the handle" readily and frequently, without what would seem to be normal provocation.

3. There is a reduced capacity for abstract thinking, and the child has difficulty in dealing with the imagined.

4. He presents easy fatiguability and distractibility.

5. He shows poor attention span and may exhibit memory defect.

6. On intelligence tests he usually shows a scattered picture, being strikingly backward in verbal tests and showing normal responses in performance tests. He is usually skillful in his movements.

These behavior and personality patterns may be due to the altered physiologic relationships of the cortex. There is no doubt, however, that these personal traits may also be the result of a psychoneurotic reaction to an environment that is lacking in understanding. Some of the children, if the difficulty is unrecognized, may become "imbeciles from deprivation." [15]

DIFFERENTIAL DIAGNOSIS

The personality and emotional problems that many of the aphasic children present may at times be even more striking than the disturbances in language function. This makes it often difficult to make a differential diagnosis between an aphasic child and a mentally retarded, schizophrenic, or autistic child.[15] Deafness, of course, is practically always a question with all these children.

A. Mental Retardation

1. Developmental history—there is a delay in the onset of sitting, walking, and talking.
2. Behavior—the child shows a limited interest in his surroundings, is easily tired, his movements are slow and awkward; the child may be placid or erethic, if the latter, he may behave like a psychotic.
3. Intelligence tests—there is an all-pervasive deficiency, although the child may present an uneven distribution of his abilities.
4. Speech is meager, and may be limited to a few irrelevant words. There is often a marked tendency to echolalia. At best, the vocabulary is scanty, and there is a meagerness of ideas.
5. Progress—there is some improvement as he grows older, but basically there is not much change, and the child remains on same level.

B. Schizophrenia

1. Developmental history—there is a normal onset of sitting and walking.
2. Behavior—odd, bizarre; there may be seclusiveness, immobility, and posturing; the child does not pay attention to his surroundings, and his mode of thinking and acting is foreign to the life of the normal child.
3. There is general emotional blunting, or the emotional response may be out of proportion to the external situation.
4. Intelligence tests—the child may be extremely backward in certain tests and surpass his own age level in others; he may be even confused with superior intelligence.
5. Speech may be very limited or it may be sparse, incoherent, and irrelevant. The child may use made-up words or odd combinations of actual words.
6. Regression in behavior and interests becomes more marked as he grows older.

C. Autism

1. Withdrawal tendencies are noted early in life.
2. There is an obsessive desire for the maintenance of sameness; changes of routine can drive him to despair.
3. The child usually shows good relation to objects, is interested in them, plays with them, but does not pay attention to persons or what people do around him—"happiest when left alone."
4. Speech—the child may remain mute, but the majority acquire the ability to speak. Speech, however, even when present, does not serve to convey meaning to others. Naming presents no difficulty; the child may remember long and unusual names. Delayed echolalia—he may repeat at a later date a word or a sentence he heard a day or two before.
5. There is not much change in his progress.

D. Aphasia

1. There is normal developmental history in sitting and walking, late in talking.
2. Behavior—there is a tendency to shyness and seclusiveness. The child reacts more or less normally to those stimuli in his surroundings which he is able to understand. Due to lack of verbal understanding, he may show at times aggressiveness and irritation.
3. Intelligence tests show a scattered picture; the child is strikingly backward in verbal tests, has normal responses on performance tests, and is skillful in his movements.
4. Speech may be absent; the child may learn to lip read or may understand gestures.
5. There is some improvement as he grows older.

As to specific tests for aphasia, there is at present no generally accepted method of testing an aphasic. Adult tests for aphasia, while they try to evaluate the patient's specific language disturbances, place a great deal of stress in evaluating the patient's disabilities in perceptual, organizational, and conceptual spheres. Since young children, and especially children who have disturbances of language function, still have not fully developed higher abstract thought processes, tests used with asphasic adults have only limited value with children.

Each aphasic child should have a complete physical and neurological examination, hearing and vision tests, evaluation of the family history and emotional status, psychometric tests, tests for various modalities of language function, and handedness determination.

TREATMENT AND REHABILITATION OF THE APHASIC CHILD

It is evident that when a child develops aphasia as a result of encephalitis, brain tumor, or abscess, our paramount concern in these cases is not the treatment of the aphasia but the treatment of the underlying condition that produces it.

The problem of aphasia, however, should be given more direct attention in those children who are either born with hemiplegia or who develop hemiplegia shortly after birth, especially if the hemiplegia is on the dominant side, which is usually the right side. It is true that cases have been reported of children who were born with right hemiplegia and yet learned to talk. Krynauw,[17] to relieve increased convulsive activity, removed the entire left cerebral hemisphere from a child with infantile right hemiplegia, and yet the child learned to speak. It is assumed that speech became possible by the use of the right hemisphere.

These children probably had the right arm so severely handicapped that they made a complete shift to the left hand.

The problem arises with the less severe cases where the hemiplegia of the dominant side is moderate or mild, so that the paralysis of the right hand is not complete. The tendency is to provide exercises for the bad arm, encourage its use, and try to improve it, even to the exclusion of the good arm. This often causes a confusion of handedness and may delay the establishment of cerebral dominance. It might be advisable not to encourage the use of the affected arm until some time after the onset of speech, and perhaps would be even better to wait until the child is progressing normally in school. This would hasten the completion of the shift to the good arm and probably aid in the establishment of dominance.

In treating the congenitally speech-aphasic child we should follow certain principles.

1. There is the principle of facilitation. Stimulation of one neuron or an area of neurons may facilitate another area through subliminal stimulation.

It has been shown that stimulation of one performance field may influence the performance in other parts of same field.

2. It has been shown that when there is damage or impairment to the brain the receptivity of the patient is reduced—it takes him much longer to react. Such a patient may succeed in a task when given sufficiently long exposure to the stimulus but fail in same task when a brief exposure is given.

3. Distractability and inability to concentrate are common traits of aphasic children. When they are being treated, distracting stimuli should be reduced to a minimum.

4. The parents must be included in the treatment program. They should be made to understand the type of defect the child has. The parents should appreciate the fact that the child has to be under observation for a long time. All of us must bear in mind that we are dealing with a growing child and that the normal process of growth and development may produce results which no one can foretell. Our efforts should be directed to help normal growth and development.

5. Finally, the most important principle in the treatment of the aphasic is that the training in each instance must be specifically adapted to the individual patient. Basically, the emphasis should be on the use of unimpaired or relatively unimpaired sensory and motor pathways, as well as on the establishment of new pathways.

The aphasic child most likely has been deluged and bombarded with all kinds of verbal stimulation in his immediate surroundings, stimulation which he cannot absorb or digest. He may have even developed resistance to the constant and persistent enticement to speak. It is perhaps better at first to reduce rather than concentrate the verbal stimuli.

Initial efforts should be directed principally toward socialization of the child, preferably in a kindergarten or nursery school with normal speaking children.

Speech skill of normal children is highest when speech is fun, when the speech situation is pleasureable, and when speech contributes to his life activities. The training must be adopted to arouse his interest and to use materials which are interesting to him.

In infancy we learn speech in terms of words and short sentences. When speech is developed, we speak and receive speech in a moving pattern of sounds in which the individual elements are disregarded.[18] As children learn to speak, they utter each pattern as a whole, for example, all gone, daddy home. The individual response is the unit, not the separate sounds or even the separate words.[19] Speech is a moving pattern of sounds, perhaps inseparable from the moving pattern of thought. Thus our aim when treating aphasic children should be not to build up speech sound by sound or later word by word, but rather to build up real speech patterns.

We should begin by presenting short words which are linked with an actual object or image and repeated with certain frequencies. At first we should start with nouns, then verbs, and, finally, adjectives. It is important to give the child encouragement and to prevent frustration.

The length of sessions should depend upon the individual child's attention span. The training should involve as many sensory approaches as possible. The child should see the object or picture, should be allowed to touch it, the name should then be pronounced to him, repeated, and perhaps even written. While this is done it should be observed whether there may be one approach by which the child learns more easily. This approach should then be combined with the approach which it is desired to improve.

The aphasics who have a serious loss in the understanding of speech—the receptive aphasics—should be taught first of all to comprehend visual cues. This may involve a simple form of lip reading, although it may not have to be carried as far as with a deaf child. A hearing tube may be tried. This tube is not used as an

amplifier, but rather to bring the auditory stimulus closer to the ear. By using this auditory stimulus in combination with visual symbols, auditory attention and perception are developed and trained.

As to the visual aphasias, there are children with severe reading disabilities where we have to accept the diagnosis of alexia (word blindness). These are uncommon cases, and at present there are no known methods to teach these children to read to any extent.

The vast majority of children with reading disabilities, however, can learn to read with special help. Ours is a literate civilization. Our system of education is built up around the reading of books. The schools are organized on the assumption that all children are ready for initial reading instruction at about 6½ years of age. Children differ, however, in their rates of development; not all children are ready to read when they attain a certain chronological age. If a child who has difficulty in learning to read is promoted from grade to grade, his confusion will increase with each succeeding grade, and he may develop an unfavorable attitude toward reading. Better adaptation of teaching methods for reading to some of these deviating cases would prevent the development of unfavorable attitudes, especially if these adaptations are made early in life. Specialists in remedial reading might well be consulted in such cases.

As for agraphia, it is practically never found by itself. Since the ability to write is dependent upon the ability to read, the child with an alexia is also unable to spell words. There is a certain sequence to language development. Hearing comprehension develops ahead of propositional speech, and learning to read precedes learning to write. Above all, we must bear in mind the interdependence of all language functions.

In conclusion, aphasia in children, especially congenital aphasia, is still an area where a great deal of investigation is needed. To say it does not exist is to bury our heads in the sand. Basic research in brain physiology and language function will undoubtedly shed some needed light on this very complex, provocative, and still unsolved problem.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Results of Three Years Experience with a New Concept of Baby Feeding. Walter W. Sackett Jr., South. M. J. **46**:358 (April) 1953.

This is a discussion of the author's concept of infant feeding based on a rigid six-hour feeding schedule and with the introduction of solid foods as early as the second day of life. Dropping the midnight feeding is advised at any time. He advises mothers to fondle and cuddle their babies only when the babies are happy, never when they are crying.

Logan, Rochester, Minn.

Unapparent Dystrophies from "A Minima" Alimentary Deficiencies (Biodietetic Researches). Georges Mouriquand, Presse méd. **61**:463 (March 28) 1953.

Although food rationing has been entirely removed in certain countries, the diet balance may prove inadequate and deceitful as regards the "maximal" substances (proteids, lipids, glucides, and minerals), as well as the "minimal" substances (vitamins, in particular). Even certain medical diets might be responsible for this. The deficiency affects mainly those children who are in a condition of accelerated growth; a condition which is often overlooked and which escapes clinical investigations.

The author carried out a series of experiments concerning, first, the deficiency, "a minima," by avitaminosis C, and second, by avitaminosis B, which are the most easily detectible.

The experiments regarding avitaminosis C show that the deficiency is not apparent until the 80th or 100th day, when severe bone lesions and manifestations similar to those of ankylosing chronic rheumatism are seen. The detection of unapparent dystrophies is facilitated by such factors as gestations, parturition, and minor intoxication.

The experiments regarding avitaminosis B were based mainly on the test of vestibular chronaxia, with pigeons fed on sterilized peeled rice, this test being the only one suited to detection of the alimentary deficiency "a minima" in vitamin B.

From the Author's Summary.

Betterment of the Quality of Milk. W. Loffler, Bull. schweiz. Akad. med. Wissensch. **9**:299 (Dec.) 1953.

An important part of the problem of the "quality of milk for human consumption" is the eradication of tuberculosis and brucellosis in our cattle population. The present campaign against cattle tuberculosis is based on a federal law of 1950. At the present time over two-thirds of the Swiss cattle population is included in the campaign, and of these about two-thirds are free from tuberculosis.

Some of the cantons will have carried out the eradication in a few years, while the total elimination throughout Switzerland may take more than 10 years. Infection with Brucella abortus is estimated to affect 6 to 11% of cows. The eradication has been started, but is encountering difficulties owing to some uncertainties in the timely diagnosis of the disease.

Considering the quality requirements as a whole, the raw milk offered to the larger marketing centers is superior to that of other European countries, but in regard to "occurrence of tuberculosis and Brucella," it is behind those countries which have freed themselves from these cattle diseases. The milk is also better from certain other points of view in the Scandinavian countries and in Holland.

Even after the elimination of bovine tuberculosis and brucellosis, raw milk cannot be consumed as a drink without appropriate preparation.

From the Author's Summary.

THE NUTRITIVE VALUE OF OVER-PASTEURIZED MILK. KARL BERNHARD, LUCIE GSCHAEDLER, and ALICE SARASIN, Bull. Schweiz. Akad. med. Wissensch. **9**:312 (Dec.) 1953.

A new process, termed uperization of milk (ultrapasteurization), has been worked out by Alpura Ltd., in Berne, Switzerland, in cooperation with Sulzer Brothers in Winterthur, by which a completely bacteria-free milk is obtained by rapid heating to 150 C. The resulting milk remains sterile and unchanged for several months when suitably stored. The taste is hardly distinguishable from that of first-class fresh milk. The biological value of uperized milk has been tested in extensive feeding experiments with rats, and its content of vitamins D, B_1, B_2, and C has been estimated. Samples were always taken of the same milk after uperization, pasteurization, and autoclaving, and the three methods of preserving milk were thus compared.

The addition of uperized milk to the basal diet produced excellent growth and normal development, which was not surpassed by the control groups with pasteurized milk. Autoclaved milk gave less favorable results, the average weight of the rats in 27- and 80-day tests being less than that of rats receiving uperized or pasteurized milk. With regard to the vitamin D content, we found no significant difference between uperized, pasteurized, and autoclaved milk. Autoclaved milk did, however, show only 65.5% (average of 13 analyses of different samples) of the amount of vitamin C present in pasteurized milk, while uperized milk contained 90.6%. The vitamin B_2 content of the milk was more definitely influenced. In the uperized milk, we found 85.5%, and in the autoclaved sample, 71.0% of the aneurin contained in the pasteurized samples. The lactoflavin content of both uperized and autoclaved milk was only very slightly less than that of pasteurized milk.

Uperized milk may be considered to be of full biological value. It is in no way less valuable than pasteurized milk; it has the advantage of complete sterility and surpasses autoclaved milk in its vitamin C and B_1 content and in its value in feeding tests. Uperization may, therefore, be regarded as a valuable new process for the preparation of a perfectly sterile milk for human consumption. The process does not have grave disadvantages and is suitable for general use.

FROM THE AUTHORS' SUMMARY.

CONSUMPTION OF MILK IN DENMARK. O. WINTHER, Bull. schweiz. Akad. med. Wissensch. **9**:334 (Dec.) 1953.

The lecture deals with the rules by which milk for human consumption is sold and controlled in Denmark, with special regard to the rationalization of milk marketing, the standardization of the fat content of milk and cream, and the organization and control of the heating of milk. There is no compulsion for the heating of milk, but, according to the Foodstuffs Law of 1952, such heating can be ordered. Practically all the milk coming to the market is heated, with the exception of the special children's milk and milk sold directly from the farms. The question of the price of milk is also discussed, as well as the methods used for bacteriological testing of heated milk.

FROM THE AUTHOR'S SUMMARY.

TESTS OF MILK, ESPECIALLY FOR BRUCELLOSIS AND TUBERCULOSIS. E. HESS, Bull. schweiz. Akad. med. Wissensch. **9**:345 (Dec.) 1953.

The procedure is described for serial tests of milk, with special regard to the culture diagnosis of Brucella abortus from the cream of test samples taken under sterile conditions. The very large amount of material (9,000 staple samples, 45,000 cows, 1,162 excretors) investigated ensures the practical experience behind this method of culture testing of milk excretors. The system of supervision described is especially suitable for a systematic campaign against Br. abortus. The extermination of individual carriers (afterbirth and milk excretors) has led to more than 50% reduction of the density of the disease within one year in the canton of Zurich.

FROM THE AUTHOR'S SUMMARY.

FUNDAMENTAL QUALITIES FOR MILK FOR HUMAN CONSUMPTION. P. MASTI, Bull. schweiz. Akad. med. Wissensch. **9**:361 (Dec.) 1953.

The directives and fundamental measures are discussed which are accepted internationally as necessary for the delivery of hygienically and qualitatively perfect milk to the consumer. The milk at present offered for human consumption in Switzerland is considered under the headings

of the significance of the feeding and health of cows, the hygiene of cows and milk, the sterilization of utensils, and the treatment of the milk for the production of first quality milk. The question of the treatment of milk by pasteurization and its delivery to the consumer in glass or in carton containers is also considered, with reference to the particular customs of the Swiss consumer and the economic conditions of the country. Finally, from the recognized international standards, conclusions are drawn for the Swiss milk industry which should be applied in the action for further improvement of the quality of milk for human consumption.

FROM THE AUTHOR'S SUMMARY.

COMPARATIVE CLINICAL RESULTS USING VARIOUS ADSORBING FOODS. M. ORLANDELLI, Clin. pediat. **35**:679 (Sept.) 1953.

During the course of the past 15 years at the Pediatric Clinic in Bologna, various adsorbing foods have been added to the feeding of infants to relieve dyspepsia and enterocolitis. These foods have included carrots, carob flour, apple pulp, and squash. Squash has proved the most efficacious of the four.

HIGGINS, Boston.

ON THE ADDITION OF A VITAMIN-CONTAINING FOOD PREPARATION TO COW'S MILK FEEDINGS. D. FUMASI, Lattante **24**:521 (Aug.) 1953.

A study was being made of the clinical value of a supplement which was added to cow's milk in amounts of 5 to 10%. The product was being sold under the commercial name of Vitadema and contained 86% carbohydrates, some protein, salts of calcium, magnesium, iron, phosphorus, and sodium and vitamins A, B_1, B_2, C, D, E, and nicotinic acid.

The babies tolerated the feedings well and gained in weight. No signs of rickets developed, and the hemoglobin percentage in the blood was well above the usual findings in babies.

HIGGINS, Boston.

CHROMATOGRAPHIC OBSERVATIONS ON THE AMINO ACID CONTENTS OF THE BLOOD AND OF THE URINE OF DYSTROPHIC INFANTS. P. CAREDDU, Minerva pediat. **5**:253 (April 15) 1953.

The amino-acid contents of the blood and urine of dystrophic infants receiving protein hydrolysate were studied by paper chromatography. The urinary excretion of amino acids was found to be greater than in infants receiving similar medication. The curve of amino acid in the blood of dystrophic infants remained elevated longer than is the case with normal infants.

HIGGINS, Boston.

THE POSSIBILITY OF PREDICTING THE CALORIC NEEDS OF AN INDIVIDUAL FROM HIS SKELETAL DEVELOPMENT. G. COTELLESSA and S. IDELL-PYLE, Minerva pediat. **5**:836 (Oct. 15) 1953.

The skeletal age, being an indication of invisible growth and development, should afford a better index for the caloric needs of a growing child than the chronological age. A typical example is given in the case of a growing girl.

HIGGINS, Boston.

PROGRESS IN THE ARTIFICIAL FEEDING OF INFANTS. ALFREDO ADAMS, Rev. españ. pediat. **9**:471 (May-June) 1953.

The author reviews the knowledge which has been gained in various countries regarding the successful artificial feeding of infants. He discusses protein, fat, carbohydrate, and mineral needs and has charts showing the quantitative and qualitative contents of various milks with regard to essential amino acids.

In Western Germany, the varieties of milk available are described, and he gives the work he did with Iligner on the anatomical and pathological change which takes place when milk containing Bacterium coli is fed to babies.

ALLEN, Santa Fe, N. M.

RETARDATION IN DEVELOPMENT: A PEDIATRIC PROBLEM. ANTONIA PRADO VERTIZ, Rev. españ. pediat. **9**:597 (May-June) 1953.

Retardation in growth is a pediatric problem and one in which the physician must be able to determine the cause and whether the tendency is reversible or irreversible. The physician is the one who can explain to the parents, alleviate guilt, and help the parents to accept the verdict.

One of the questions a doctor should ask himself is, "Is the cause a genetic factor?" Under genetic factors, the child's growth retardation may be in a proportional manner or his growth may be disproportional. There are constitutional and racial factors which will result in a slow growth, which is perfectly natural, and no effort should be made to push the growth curve in such a child. In achondroplasia and osteogenesis imperfecta, the prognosis is as fixed, but with different implications for future pregnancies.

Under factors of nutrition, circulation, and respiration, the author includes the celiac syndrome, fibrocystic pancreas, chronic renal insufficiency, congenital cardiopathies, etc.

Under hormonal factors, the subdivisions include hypofunction and hyperfunction of the endocrine system. Under hypofunction, the thyroid, pituitary, gonads, and hypoinsulinism are included. Under hyperfunction, the gonads and suprarenals are of the greatest importance at this age.

Retardation, of course, may be a result of the combination of any one of these group classifications. Several case reports are included where the prognosis is varied and the detail of all the diagnostic aids explained. The doctor must be sure there is no cardiac, thyroid, or other deficiencies and must always think of tumors, especially in the suprarenal glands.

ALLEN, Santa Fe, N. M.

CORRELA MILK IN THE ARTIFICIAL NUTRITION OF THE INFANT. VERA GAUPP, Med. Klin. **48**:407 (March 27) 1953.

Correla milk is a dry milk preparation which, in its composition, approximates human milk in the correlation of albumin, casein, fat and sugar. Vitamins A, D_3, B_1, and C are added. The mineral salts are also considered. When human milk is not available, the preparation can be recommended for healthy newborns and infants, for prematures in the form of mixed milk, and beyond the first weeks of life exclusively.

AMBERG, Rochester, Minn.

THE FATE OF INFANTILE DYSTROPHIES AND ATROPHIES AND THE FIRST CHILDREN'S CLINIC OVER A PERIOD OF 20 YEARS. J. HNATEK and V. MYDLIL, Pediat. listy **8**:28, 1953.

Stress is laid on the importance of a complete diet with 6 to 8.5 gm. of protein per kilogram of body weight a day and the early addition of fats.

Stress is also laid on the great importance of perfect hygienic hospital conditions and on treatment to combat infection (antibiotics).

FROM THE AUTHORS' SUMMARY.

CYSTINE STORAGE DISEASE WITH AMINOACIDURIA AND DWARFISM (LIGNAC-FANCONI DISEASE): V. THE OPHTHALMOLOGY OF LIGNAC-FANCONI DISEASE. A. A. DOUGLAS and H. BICKEL, Acta pædiat. Supp. 90, p. 106, 1953.

The ophthalmological appearances in five cases of Lignac-Fanconi disease have been studied. In every case, crystalline deposits were seen in the cornea and the conjunctiva and in two cases in the iris, but never in the lens, vitreous humor, or other media of the eye. Massive deposition was easily recognizable by loupe and may even be suspected by naked-eye examination. In less developed cases, the crystalline deposits were visible only by use of a slitlamp; the application of this technique in uncooperative children is described.

Microscopy of a conjunctiva biopsy specimen revealed that the crystals were partly hexagonal, their localism being intracellular and extracellular. The ninhydrin test gave a diffusely positive reaction. X-ray diffraction photography of the biopsy specimen showed the pattern to be entirely characteristic of pure crystalline cystine. In two patients with severe photophobia, epithelial lesions of the cornea were shown by staining with fluorescein. This change was absent in the

patients without photophobia and is, in our opinion, the immediate cause of the photophobia. The eye appearances in Lignac-Fanconi disease are sufficiently characteristic to eliminate any serious diagnostic difficulty.

FROM THE AUTHORS' SUMMARY.

CYSTINE STORAGE DISEASE WITH AMINOACIDURIA AND DWARFISM (LIGNAC-FANCONI DISEASE): VI. DETAILED CLINICAL AND BIOCHEMICAL REPORT ON TWO BROTHERS SUFFERING FROM LIGNAC-FANCONI DISEASE. M. G. PHILPOTT, C. C. HARVEY, and E. FINCH, Acta pædiat. Supp. 90, p. 114, 1953.

The case records of two brothers suffering from Lignac-Fanconi disease are given in detail. Two further siblings probably suffered from the disease. The results of certain special investigations are discussed. In a mineral balance we have not been able to prove that the hypophosphatemia in one of the cases was due to an excessive excretion of phosphorus.

In both brothers, the glutamic-acid level in the serum was found to be raised. This supports the view that a disorder of amino-acid metabolism is the underlying cause of the disease. It is suggested that the large quantity of amino acids passed by the kidneys has a nephrotoxic action. The pathogenesis of other features of the disease can be explained by dysfunction of tubular reabsorption caused by this action, and the ultimate onset of renal failure can be explained by the same action involving the glomeruli.

With alkali therapy, the general condition of both boys has improved, although a normal plasma CO_2 combining power could not be reached in either case. High vitamin D dosage has produced some healing of the skeletal changes, but attention is drawn to the possibly dangerous effects of this treatment. One case died from heart failure secondary to renal failure after three months' treatment.

The genetics of the disease are discussed. The evidence presented from our cases seems to confirm the theory of a recessive inheritance.

FROM THE AUTHORS' SUMMARY.

CYSTINE STORAGE DISEASE WITH AMINOACIDURIA AND DWARFISM (LIGNAC-FANCONI DISEASE): VII. SOME BIOCHEMICAL ASPECTS OF LIGNAC-FANCONI DISEASE. H. BICKEL and E. M. HICKMANS, Acta pædiat. Supp. 90, p. 137, 1953.

Phosphorus and calcium balances in three patients of this series are analyzed and compared with eight balances in the literature. Four of the 11 were carried out under vitamin D influence and were positive. Of the remaining seven, five phosphorus and two calcium balances were negative. This was due to phosphorus and calcium loss in the feces; neither hyperphosphaturia nor hypercalciuria was detected. The balances in Lignac-Fanconi disease were identical with a balance performed in a case of resistant rickets. Compared with renal rickets, the hypocalcemic, hyperphosphatemic, or normophosphatemic forms of Lignac-Fanconi disease show certain differences. Though the excretion of phosphorus and calcium in the urine was decreased in both conditions, the hypocalcemia in Lignac-Fanconi disease was more marked and the hyperphosphatemia mild or absent. It is suggested that the mechanism of these biochemical changes is different from that in renal rickets.

Chromatographic studies of urine and plasma in patients with Lignac-Fanconi disease showed a moderate to strong increase of 10 to 20 amino acids in the urine, while in the plasma, the amino-acid pattern was normal, though the concentration of the amino acids seemed to be above the normal range. Microbiological assay of 12 amino acids by Dr. Schreier showed up to a twentyfold increase of various amino acids in the urine and up to a 100% increase in the plasma. Estimations of glutamine and glutamic acid by Professor Krebs showed similar results. These findings do not indicate primarily a renal mechanism of the aminoaciduria, but suggest a prerenal disturbance of the amino-acid metabolism.

Electrolyte studies in two patients under normal conditions and after acid feeding point to a complex disturbance of the acid-base metabolism. Several factors seem to be involved, namely, increase of organic acids in the urine and probably in the blood, insufficient ammonia production by the kidney, loss of the fixed bases sodium and potassium, and faulty reabsorption of bicarbonate. The relative importance of these factors is discussed.

No satisfactory explanation of the "glucose shock" in Lignac-Fanconi disease has so far been offered. During three glucose tolerance tests we followed the potassium level in the plasma of our patient and of a healthy control. Glucose ingestion resulted in pronounced and prolonged hypopotassemia in our patient, which was not due to potassium loss in the urine. In the control, the response was similar but milder and briefer. We suggest that the "glucose shock" in Lignac-Fanconi disease is a "hypopotassemic shock."

FROM THE AUTHORS' SUMMARY.

CYSTINE STORAGE DISEASE WITH AMINOACIDURIA AND DWARFISM (LIGNAC-FANCONI DISEASE): VIII. MORBID ANATOMY, HISTOLOGY, AND PATHOGENESIS OF LIGNAC-FANCONI DISEASE. H. S. BAAR and H. BICKEL, Acta pædiat. Supp. 90, p. 171, 1953.

Detailed gross anatomical and histopathological findings in six cases of Lignac-Fanconi disease are described and discussed. An attempt is made to present the natural history of individual organ changes, particularly those of the kidney. It is interesting to note that the disease in its early stages can occur without kidney changes. The bone changes are essentially rachitic; there is no feature of the histopathology of the bones which is not met with in rickets, particularly in "rachitis tarda." Bone change suggestive of hyperparathyroidism are not conspicuous in this disease. The parathyroids were markedly hypertrophic in two of our cases; hypertrophy in other cases cannot be excluded.

The phosphatase reaction was negative in all the kidneys examined, reduced in the liver, spleen and bone marrow, but normal in the small intestine. Negative phosphatase reaction in the kidney has also been found in chronic inflammatory kidney disease and is not specific for Lignac-Fanconi disease.

Methods for demonstration and identification of cystine crystals in tissue sections, bone-marrow films, and lymph-node imprints are described, together with experiments which account for the difference between the crystallographic appearance of cystine in tissues and cystine crystallized from aqueous solutions. In our opinion, a lymph-node biopsy is the most reliable procedure for a definite diagnosis of Lignac-Fanconi disease in vivo, though bone-marrow sections and/or films are usually sufficient for the purpose.

The intracellular localism of cystine crystals is stressed, and histopathological and experimental evidence is given for the assumption that cystine storage is not due to phagocytosis, but that cystine crystallizes at the site of its formation, namely, in a certain part of the reticulo-endothelial system.

A critical review is given of various hypotheses concerning the pathogenesis of Lignac-Fanconi disease. The hypothesis is put forward that Lignac-Fanconi disease is a disorder of protein metabolism, probably of its anabolic phase. As a disorder of intracellular metabolism, the disease is likened to true lipidoses.

FROM THE AUTHORS' SUMMARY.

Vitamins; Avitaminoses

COMPARISON OF CHEMICAL ANALYSIS AND BIOASSAY AS MEASURES OF VITAMIN A VALUE: YELLOW CORN MEAL. E. C. CALLISON, L. F. HALLMAN, W. F. MARTIN, and E. ORENT-KEILES, J. Nutrition **50**:85 (May 11) 1953.

Callison and co-workers presented bioassay data for the vitamin A value of both corn meal and corn meal extract. The vitamin A value of the corn meal was 264 I.U. per 100 gm., whereas the extract of 100 gm. of the meal had a value of 324 I. U. The biological vitamin A value of the corn meal extract agreed within the limits of experimental error with that anticipated from chemical analysis of the corn meal; i. e., 324 and 317 I. U. per 100 gm., respectively.

The availability to the rat of the biologically active carotenes of yellow corn meal appears from this study to be high; i. e., 82%. It is suggested that the poor availability reported by other investigators may be accounted for by the inclusion of considerable amounts of inactive pigments with the B-carotene fraction.

FREDEEN, Kansas City, Mo.

RICKETS, DEFICIENCY OF "ALKALINE" PHOSPHATASE ACTIVITY, AND PREMATURE LOSS OF TEETH IN CHILDHOOD. EDNA H. SOBEL, L. C. CLARK JR., R. PHYLLIS FOX, and MEINHARD ROBINSON, Pediatrics **11**:309 (April) 1953.

A child, studied between the ages of 1½ and 3½ years of age, presented an abnormally low plasma alkaline-phosphatase activity (0.8 to 1.64 Bessey-Lowry), a deformed skeleton, and the loss of most of her deciduous teeth. The serum Ca was normal; the serum inorganic phosphate remained at the normal relatively high levels of infancy as the child grew older. Roentgenograms demonstrated deficient mineralization of the skeleton and teeth. Biopsies of the liver and the costochondral junction displayed a deficiency of tissue alkaline-phosphatase activity. The architecture of the rib was consistent with rickets. There was no evidence for the presence of an inhibitor of alkaline phosphatase, such as beryllium, or for an excessive excretion of the enzyme. Treatment with purified growth hormone, ascorbic acid, and thiamine chloride had no effect, while 500,000 units of vitamin D caused little change in the enzyme activity in a 10-day period. The father had low plasma alkaline-phosphatase activity, and a number of similar patients are mentioned for whom there was also evidence that the deficiency in alkaline-phosphatase activity may be genetically determined.

While the precise role of alkaline-phosphatase activity in the metabolism of bone is not clear, the findings in this patient suggest that growing bone may require the presence of alkaline phosphatase for normal calcification and that the skeletal disorder, which could not be distinguished from rickets, may be related to a disturbance in the local factor.

FROM THE AUTHORS' SUMMARY.

ABSORPTION OF VITAMIN A ALDEHYDE BY CHILDREN. CHRIS P. KATSAMPES, AUGUSTA B. MCCORD, ROBERT N. JAMBURGER, and SAMUEL W. CLAUSEN, Pediatrics **12**:191 (Aug.) 1953.

Vitamin A aldehyde is readily absorbed and converted into vitamin A alcohol by the normal human subject. It is, therefore, a good source of vitamin A for man. Inasmuch as patients with fibrocystic disease of the pancreas show poor absorption of vitamin A acetate and much better absorption of vitamin A aldehyde and vitamin A alcohol, while children with celiac disease show poor absorption of all three forms of vitamin A, the vitamin A-aldehyde absorption test is a new aid in establishing the differential diagnosis of these two diseases. The absorption of vitamin A aldehyde by patients with various other diseases usually parallels their absorption of the acetate and the alcohol.

FROM THE AUTHORS' SUMMARY.

PROPHYLAXIS AND TREATMENT OF RICKETS WITH VITAMIN D MILK. HANNAH UFLACKER, Monatsschr. Kinderh. **101**:38 (Feb.) 1953.

Thirty healthy infants, ranging in age from 10 days to 5 months, received milk containing vitamin D_2 for an average of 12.3 months (six months to two years). No clinical, radiological, or blood-chemical evidence of rickets was found in 25 patients after this period. In five children, transient craniotabes, lasting four to six weeks, developed as the only sign of rickets. Of these five patients, four had been premature births, of which three were mulattoes, and one patient had had repeated upper respiratory infections. The average daily dose of vitamin D_2 in the milk was 500 units.

Six infants with florid rickets were cured within four to six weeks by receiving, during this period, milk containing a total of 15,000 to 22,000 units of vitamin D_2.

The author believes that vitamin D_2 milk is a more effective antirachitic agent than oily preparations or pulvules of vitamin D.

HARTENSTEIN, Syracuse, N. Y.

Hygiene; Growth and Nutrition; Public Health

CHRONIC EOSINOPHILIA. C. G. LOPEZ, N. N. ALIMURUNG, and V. DE LA LUENTE, Philippine J. Pediat. **2**:22 (July-Sept.) 1953.

A case is presented in which the syndrome of chronic eosinophilia, pulmonary changes associated with fever, hyperleucocytosis, and eosinophilia, hyperglobulinemia, and hepatomegaly is shown.

It is highly probable that there are eosinophilic granulomatous lesions of the liver in the presence of Ascaris infestation. The pulmonary manifestations are assumed to be of a similar nature.

An allergy to Ascaris plays an important part in the production of this clinical entity. The tissues manifest a hyperergic tissue response to the presence of the antigen-producing larvae found within, which is designated as visceral.

It is a relatively benign disease; its severity varies with the number of Larva migrans in the tissues and the allergic state of the infected person.

A unique feature of this case, which has not been shown by a reported case in literature, is the finding of ascitic fluid, which is an exudate with numerous eosinophiles.

This syndrome has been related to the group of disorders which include Löffler's syndrome and tropical eosinophilia.

As regards treatment, nothing is definitely known. Diethylcarbamazine (Hetrazan) and arsenicals were advocated. In this case, Acetylarsene and an arsenic preparation (Pentarsolo) were tried, with no significant results.

FROM THE AUTHORS' SUMMARY.

PATTERN OF CHILDREN'S DISEASE AND DEATH AS SEEN IN A CHILDREN'S HOSPITAL AT COLOMBO, CEYLON. C. DE SILVA, O. C. RAFFEL, and PRIYANI SOYSA, Acta pædiat. **42**:453 (Sept.) 1953.

Intestinal parasitism was the chief cause of ill health in children in the hospital. Ascaris lumbricoides was the commonest intestinal parasite and the Trichuris trichiura was the second. The incidence of intestinal parasitism rose with each year of life and was extremely high at 5 years and over.

Nutritional disorders were common, including many cases of fatty liver and edema as well as of vitamin A and riboflavin deficiencies. A pre-Bitot pigmentation, which was often the precursor of a Bitot pigmentation, and a "gutter" pigmentation of the lower part of the sclera are described. The former was a vitamin A deficiency and the latter was probably due to combined vitamin A and riboflavin deficiencies.

Among the respiratory diseases, bronchopneumonia caused a high fatality rate in the age group below 5 years.

Gastrointestinal disorders showed a peak in incidence during the first year of life, the fatality rate was high also in following years. Salmonellosis was a common cause of diarrhea in infancy and early childhood.

The vast array of preventable diseases is heartrending. All possible forces and resources of the country should be marshalled and put into action in order to reduce the unnecessary suffering and sorrow caused to children by poverty, superstition, ignorance, wrong food habits, and pernicious teaching by those who should know better.

FROM THE AUTHORS' SUMMARY.

Prematurity and Congenital Deformities

ADRENAL FUNCTION IN PREMATURE INFANTS: II. ACTH-TREATED INFANTS AND INFANTS BORN OF TOXEMIC MOTHERS. JONATHAN T. LANMAN, Pediatrics **12**:62 (July) 1953.

The urinary formaldehydogenic steroid excretion was measured in five corticotropin (ACTH)-treated premature infants and in three premature infants born of toxemic mothers. One of these toxemic mothers received no therapy, one received corticotropin ante partum, and one cortisone ante partum. Na, K, and N balance studies were conducted in three of the above infants.

Steroid excretion rose during corticotropin administration and fell two to four days after discontinuance of corticotropin therapy. The fall was followed by a moderate rise, or rebound, in some cases. These findings indicate that the adrenals of young infants have a functional reserve and are capable of responding to either an increase or a decrease in the adrenocorticotropic stimulus by a corresponding change in steroid production. This response resembles that seen in normal adults, and is further evidence that this aspect of adrenal function is not impaired during involution of the fetal adrenal cortex.

Corticotropin administration in one infant produced an increase in sodium excretion during the first 16 days of therapy. This response is the opposite of that usually found in normal adults and confirms a similar previous finding reported by Klein. Under continued corticotropin therapy, the infant ultimately retained Na, as does the normal adult. The cause for this early abnormal response is unknown, but it resembles one seen in adults with Cushing's disease in whom desoxycorticosterone induces a loss of sodium.

The infant born of the cortisone-treated toxemic mother had normal postnatal urinary steriod values; the infant born of the corticotropin-treated toxemic mother had unusually high postnatal values. These observations suggest that cortisone failed to cross the placenta in sufficient quantity to influence steroid excretion of the infant, but that corticotropin administered to the mother reached the fetus and stimulated his adrenals.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL MALFORMATIONS AND BIRTH INJURIES IN NEW YORK CITY. HELEN M. WALLACE, LEONA BAUMGARTNER, and HERBERT RICH, Pediatrics **12**:525 (Nov.) 1953.

In 1951, a total of 1,501 children was reported to have been born alive with one or more congenital malformations, an over-all reported incidence of 9.2 per 1,000 live births. Two-thirds of the babies were delivered by a private physician in a hospital and one-third on a ward service in a hospital. The incidence in the two groups and in white and nonwhite babies was approximately the same. However, the incidence in babies weighing less than 2,500 gm. was twice that in those babies weighing more. Club foot, dactylism, cleft palate and/or harelip, and hypospadias were the most frequent types of congenital malformations reported, accounting for 78% of the total reported. There were 128 babies reported with cleft palate and/or harelip, an over-all incidence of 0.79 per 1,000 live births. The effect on neonatal mortality is presented.

In 1951, a total of 377 children was reported to have been born alive with one or more birth injuries, on over-all reported incidence of 2.3 per 1,000 live births. One-half were reported with severe birth injury. The reported incidence was the same regardless of type of patient (private or ward service), color, or birth weight.

The 1951 data for New York City are compared with similar data for upstate New York for 1940-1942. The over-all incidence in reported congenital malformations in the two groups is similar, although some differences occurred in the frequency of individual malformations. The over-all incidence of reported birth injury in upstate New York was more than three times that in New York City; the incidence of each type of birth injury was higher in the upstate group. The use of such data in planning services for these children in a community is discussed.

FROM THE AUTHORS' SUMMARY.

CLEIDOCRANIAL DYSOSTOSIS. DAVID EISEN, Radiology **61**:21, 1953.

Four cases with the more or less characteristic changes in the bones and membranes, namely, defective or absent clavicles, wide sutures, delayed closure of the epiphyses, retarded ossification, irregular capital epiphyses, and many other changes, are described or illustrated. Of the author's cases, three were from one family. A father, a daughter 3 years of age, and an infant son. This report is of special interest, as it shows the x-ray findings in three cases at an unusually early age, that is, 3 months, 16 months, and 4 years. Seldom has the diagnosis been made so early in life.

The author emphasizes the fact that the entire skeleton is affected to a greater or less degree. This reviewer first called attention to the widespread skeletal changes, in 1933. Since then, 15 cases have been seen showing the changes illustrated here.

ANSPACH, Riverside, Ill.

CONGENITAL HEREDITARY CRANIUM BIFIDUM OCCULTUM FRONTALIS. RAYMOND J. TERRAFRANCA, and ALLAN ZELLIS, Radiology **61**:60, 1953.

A 6-year-old Negro girl was found to have a "soft spot" 5.0 cm. by 3.5 cm. in diameter in the midfrontal area of the skull. This presented an area devoid of bone on skull roentgenograms. An older brother (aged 14) showed similar changes. The mother (aged 37) gave a history of

similar "soft spots" earlier in life, but at the time of examination they had hardened. X-rays showed thin bone over this area. There were indications of spina bifida occulta and enlarged parietal foramina in all three patients. The author considers the condition hereditary, as well as congenital.

ANSPACH, Riverside, Ill.

EMBRYOPATHIES CAUSED BY VIRUS INFECTIONS DURING PREGNANCY. GIAN TONRUDY, Études néo-natal. **2**:107 (Sept.) 1953.

In this study, the effect of the rubella virus on the human embryo is described. Ten human embryos of different ages are studied whose mothers had been attacked by rubella between the 35th and 51st days of pregnancy. According to our observations, the rubella virus penetrates from the maternal bloodstream through the intact chorioepithelium. Consequently, the human embryo is not affected by a generalized disease, but only certain organs—the lens, the epithelium of the inner ear and the enamel organs—are infected, and a destructive effect results. There exists an evident organ affinity.

The destruction consists of the dismixture in drops and vacuolar variation of the cytoplasm, with following pyknosis of the cell nucleus. It does not appear at the same time in the above-mentioned organs; 17 days after the mother's disease, the lens fibers show degeneration, whereas not until 222 days after the mother's infection by rubella, are the sensory cells of the inner ear and the cells of the enamel organs visibly destroyed. According to our observations, we assume that the virus attacks the epithelial cells of the lens, the auditory vesicle, and the enamel organ in the premature embryonic state and increases therein. It only becames evident when the cells reach their state of differentiation, which is connected with great activity of their metabolism. With regard to this fact, the effect of the rubella virus is phase-specific. It probably interferes with the metabolism of the cells and produces the hyaline droplets of the cytoplasm and the cellular pyknosis.

Our observations have proved that the disturbances caused in the fetus attacked in embryopathia rubeolosa are not specific. Also, the virus of epidemic parotitis, epidemic hepatitis, and poliomyelitis produce the same effect, i. e., their virus infiltrates the cells of the lens vesicle and produces a disturbance of the growth of the fibers.

FROM THE AUTHOR'S SUMMARY.

RETINOPATHY (RETROLENTAL FIBROPLASIA) IN PREMATURE INFANTS: DISCUSSION. A. MINKOWSKI and B. AUVERT, Presse méd. **61**:653 (May 6) 1953.

Retinopathy or retrolental fibroplasia in premature infants has been recognized to be an essential cause of blindness. Its etiology is still mysterious and raises some problems of vascular physiopathology and oxygen and hydroelectrolytic metabolism.

Conclusions as stated by certain workers seem at times, too absolute and univocal, all of them trying to find only one cause for retinopathy.

The authors' opinion is that the condition is a complex one, due probably to multiple causes and developing on an elective terrain, which is the underweight child.

They review and discuss the various causes suggested, and obtain from their study some practical inferences, such as the maintenance of oxygen therapy, the preference for maternal milk in the infant's feeding, possibly the contraindication for blood transfusions, and the reduction of fluids when the lesions are in full development.

FROM THE AUTHORS' SUMMARY.

DYSOSTOSIS CLEIDOCRANIALIS. A. ZANINI and L. PARENZAN, Minerva pediat. **5**:194 (March 31) 1953.

A boy 3 years of age had a broad head with a circumference of 52 cm., a widely open fontanelle, and imperfectly joined cranial sutures; the right clavicle was rudimentary, permitting exaggerated shoulder movements, and the child's height was 83.5 cm., as compared with a normal of 89.8 cm. There were abnormalities on the growth centers of the humerus, ulna, and radius and of the metacarpal and metatarsal bones. There was no history of similar abnormalities in the ancestors or collaterals. No disturbances of the thyroid or adrenal glands were detected.

HIGGINS, Boston.

OSTEOCHONDRODYSTROPHY IN GROWTH: ONE CASE OF BRAILSFORD-MORQUIO'S DISEASE AND TWO CASES OF PFAUNDLER-HURLER'S DISEASE. P. TOLENTINO and G. COTELLESSA, Minerva pediat. **5**:791 (Sept. 30) 1953.

A detailed chart is depicted classifying the various types of osteochondrodystrophy; the primary division is into three groups, those due to early closure of the epiphysis, those due to delayed ossification, and those due to dysgenesis of the epiphysis and the metaphysis. In this last group belong Morquio's disease and gargoylism, cases of which are reported in considerable detail. In differentiating between the two conditions, one notes that in gargoylism both the wormian and the epiphyseal bones are involved, while only the epiphyseal bones are abnormal in Morquio's disease. There are mental retardation, splenomegaly, frequent corneal opacity (75% of cases), occasional deafness, pathological leucocytes, swollen epiphyseal junctions, and a fatty thick skin in gargoylism, but not in Morquio's disease. The dysgenesis in gargoylism is accompanied by lipid deposits and appears to be of metabolic etiology, while Morquio's disease it may be called "pure" dysgenesis.

HIGGINS, Boston.

PRENATAL INTOXICATIONS. HANS MAUTNER, Wien. klin. Wchnschr. **64**:646 (Aug. 29) 1952.

Two boys are reported with severe mental deficiency. The mothers of both children tried to produce abortion, one by taking "cotton wood" pills (cortex radicis gossypii), the other by taking a large dose of quinine. These cases are not cited as proof of the prenatal influence of the drugs on development, but such an effect is regarded as very possible.

AMBERG, Rochester, Minn.

THE PROGRAM FOR PREMATURE INFANTS IN GOTHENBURG, SWEDEN: THE PRINCIPLES OF TREATMENT AND THE RESULTS OBTAINED. K. HOLMDAHL, Acta pædiat. **41**:1 (Jan.) 1952.

Since the beginning of the year 1948, distinctly improved results have been achieved in the care of premature infants in Gothenburg. An account is given of some new principles of treatment. The value of oxygen administration, particularly gastrointestinal administration, and the theoretical and practical advantages of human colostrum as a nourishing medium for the premature infants are stressed.

In order to judge the results of care, the mortality in three other series of premature infants is compared with the author's own series. An analysis of the mortality in the different weight groups shows that a very favorable figure was reached in the Gothenburg series in the weight group 1,510 to 2,000 gm. For the weight groups 1,010 to 1,500 and 2,010 to 2,500 gm., the mortality was lowest in the series from Denver.

From the distribution of deaths with a considerable peak immediately after birth and from the nature of the causes of death, it appears that disturbances of nutrition and infections were seldom the cause of death.

A more substantial reduction of the mortality for premature infants in Gothenburg is only possible by reducing the mortality in the first 48 hours. An intensified cooperation between pediatricians and obstetricians is necessary.

FROM THE AUTHOR'S SUMMARY.

THE PREMATURE CHILD. SIGRID DAAE BLEGEN, Acta pædiat. Supp. 88, p. 7 (Jan.) 1953.

1. The Frequency of Premature Births in Oslo During the Period 1930-1939.—Of all the children born to mothers resident in Oslo at public clinics here during the above-mentioned period, 6.7% were premature. Of all children born alive, the prematures comprised 5.4%, as compared to 47.7% of stillbirths. During the corresponding period there were only a couple of cities in Sweden and Denmark (Stockholm and Roskilde) where the figures were equally low. This result is found in spite of the fact that the lowest limit toward miscarriage in the Oslo group is 400 gm. This limit is lower than that generally used in Europe and corresponds to the lowest American limit.

The sex distribution among prematures in Oslo corresponds to that usually found, namely, more females than males.

Over half of the premature children in Oslo had a birth weight of 2,001 to 2,500 gm. (56.5%), while only about 20% fall in the weight groups 1,500 gm. or less. The weight distribution of

prematures born alive shows an even greater excess for the weight class 2,001 to 2,500 gm. A similar distribution was found earlier in Oslo by Sunde, but in publications from other localities, relatively more prematures are found in the lowest weight classes.

2. The Causes of Premature Birth.—In 38% of the cases it was not possible to demonstrate the cause of the premature birth. Maternal causes were found in 32%. Toxemia was found the largest group (syphilis was found in only 1%). Placental causes and multiple births followed in frequency. Of the 1,127 premature children, 18.8% were twins or triplets, but in only 9.6% was the multiple birth the only known cause of prematurity. In the other cases, the multiple births were combined with toxemia or placental complications. Among the full-term children born in Oslo in the same clinics during the same period, only 1.6% were twins or triplets.

These figures are in good agreements with those found elsewhere.

It has further been demonstrated that a larger number of premature children were firstborn than in a normal group. There were relatively more mothers of premature children under 20 and over 30 years of age than mothers of mature children, i. e., premature birth was relatively frequent in very young mothers and in primiparas over 30.

Premature births were almost twice as frequent among unmarried mothers as among married ones. It was also found that prematurity was more frequent under poor living conditions than under adequate ones.

Age is certainly an important factor for the unmarried mothers, as well as the fact that most of them are primiparas.

The relation between the age of the mother, the birth order of the child, and premature birth otherwise agrees with the literature.

The influence of social factors also agrees with more recent American and English publications. In America, particularly, the significance of diet for the frequency of prematurity has been emphasized. It is claimed that proper diet during pregnancy will not only reduce the number of premature, but will especially reduce the number of prematures with very low birth weights.

There are relatively fewer prematures in Oslo than are reported from American or English cities, and fewer prematures with very low birth weight, and this is probably because slums are practically nonexistant in Oslo. Those who are classified in the lowest social classes have, nevertheless, in most cases had a fairly good diet. All have had the opportunity of free medical examination at control antepartal clinics, where they also obtained advice as to diet, etc.

3. Stillbirths and Mortality.—In about 21% of all premature births, the infants were stillborn, while the corresponding figure for full-term deliveries was 1.6%, i. e., stillbirths were about 13 times as frequent in premature as in full-term births. On the other hand, there was no difference in the frequency of stillbirths for married and unmarried mothers.

The higher stillbirth frequency among prematures is in agreement with previous reports. But a uniform stillbirth frequency for married and unmarried mothers does not agree with more recent investigations from England and Scotland. There it has been found that the stillbirth frequency is twice as high when the mothers have lived under poor conditions as when they have lived under satisfactory ones. It may be assumed that the majority of unmarried mothers live under difficult social conditions. Since the stillbirth frequency in the present investigation was not greater for unmarried than for married mothers, this may be because the unmarried mothers were, on the whole, younger than the married ones, and also because the difference in standard of living is not as great in Norway as in England and Scotland. Moreover, there was readily accessible free medical advice during pregnancy, and medical assistance at delivery was the same for both groups.

It was demonstrated that the risk of death was much greater for premature infants than for those from normal pregnancies. The difference was greatest during the first year of life; later it was less pronounced. During the first year of life, the neonatal period was the most critical. Of the premature children who died during the first year, 81% died in the neonatal period (46.3% during the first 24 hours). Of all prematures born alive, 9.9% died during the first 24 hours, while the corresponding figure for a normal series was 0.9%.

Mortality was greatest among the prematures with a low birth weight, so that no premature infant with a birth weight of 1,000 gm. or less lived more than a month. There was some excess

of mortality among premature children whose mothers came from a poor social background (unmarried mothers), and this was most marked in the period after discharge from the clinic, during the child's first year, but was less pronounced subsequently.

A good many of the causes of death of the prematures were directly related to prematurity. In these cases the diagnosis was "congenital debility." The next most frequent causes were hemorrhages of the brain and of the cerebral membranes. After the first year of life, infections were the most frequent cause of death.

An increased frequency of stillbirths and "total mortality" was also demonstrated where the mother had complications during pregnancy or delivery.

These results on the frequency of stilbirths and mortality are in general agreement with earlier findings. The higher stillbirth frequency in the Oslo group as compared with some English publications is due to the fact that the latter use a limit of 28 weeks above miscarriage, while the present group includes prematures with a birth weight down to 100 gm.

There is no great difference in neonatal mortality between the Oslo material and American and English figures, but in the lower weight groups the mortality is a little higher in Oslo. It is reasonable to assume that this difference is due to varying opportunities for special care of prematures. It is particularly likely that the deaths classified under the diagnosis "congenital debility" could be reduced considerably by special and trained personnel.

The stillbirth frequency was lower for premature twin and triplet children than for single children, but the mortality was the same.

4. The Mental Development of Prematures.—Of the 541 premature children about whom information was obtained through 1948 and 1949, when the control examination was made, there were as least 4.6% with an I. Q. of 70 or lower. Of the 534 premature children who were registered at ordinary primary schools, 7.5% were special-school pupils. There were relatively more prematures among the pupils of the special schools than among the pupils of the Oslo primary schools in the school year 1946-1947. The majority of the prematures were from the poorest residential districts, from which the largest number of the special-school pupils were recruited. There was no marked deviation in age for the premature children as compared to the normal age in the classes in the ordinary primary school.

There was a marked correlation between the social background of the premature children, rated according to housing conditions, and their scholastic achievements and character. The percentage of repeaters was decidedly less among prematures from the best social background than among those who lived under poor housing conditions. In the school year 1946-1947, however, there was no marked difference in the percentage of repeaters between the prematures and ordinary school children.

When the scholastic achievment and personal material of the prematures was compared with control material from a corresponding social background, a slight difference was found. This difference was in favor of the control material. The scholastic achievement of the premature girls was somewhat better than that of the boys. There was no pronounced difference in mental development for the prematures with the lowest and highest birth weights. None of the prematures with a birth weight of 1,500 gm. or less could be classified as feeble-minded.

Compared with reports in the literature, this shows that the mental development of the premature children in the Oslo material is considerably better than earlier investigations have indicated. Some more recent investigations from America show even more favorable results. This improvement is probably due to the better opportunities for special care during the earliest period and continued control for the American prematures all the way up to school age.

5. The Physical Development of Prematures.—The average height and weight for premature children in Oslo born during the period 1930-1939 are somewhat lower than those for ordinary school children in Oslo during the same period. The oldest children were followed until they were 14 to 15 years old. When social differences were eliminated by comparing premature children with others from as similar a background as possible, the prematures still had a lower height and weight than other school children, and there was no tendency to compensation toward puberty. The difference, however, was so slight that the figures were within the normal variation in the individual age classes.

6. Malformations, Defects, and Nervous Manifestations in Premature Children.—The distribution of various anomalies in prematures in Oslo was about the same as that found elsewhere. Eye anomalies, nervous manifestations, and hernia were the most frequent. There were no cases of retrolental fibroplasia. Little's disease was found in 0.4%, while previous authors have reported a considerably higher frequency. This may be connected with the weight distribution in the different materials.

7. Conclusion.—All the evidence indicates that good living conditions during pregnancy and medical control throughout the entire period both reduce the number of premature births and cause relatively more of the prematures born to be viable. It is, therefore, of the greatest importance, to continue to establish and extend the activity of control clinics for pregnant women and to see to it that they are instructed as to proper diet and way of living. It would be possible to reduce mortality among the prematures by having specially trained nurses at the maternity clinics to care for these premature children. A single clinic could be a center where prematures from the entire district would receive care, as has been done in America. Moreover, it must be regarded as certain that the continued care of premature infants after discharge from the clinic, especially during the first 2 to 3 years, as regards diets and hygiene, is of basic significance for their future mental and physical development. If special control clinics could be established for these children, where there were also possibilities for helping the needy, the difference between full-term and premature children later in life would probably be reduced considerably.

This holds for premature children who have not suffered injury at birth which has caused irreparable harm. However, this occurs so rarely that no efforts should be spared to ensure a minimum mortality among premature children.

FROM THE AUTHOR'S SUMMARY.

RETROLENTAL FIBROSIS. TORE LIE TOMASEN, Tidsskr. norske lægefor. **71**:350 (May 15) 1951.

The first two cases of retrolental fibrosis seen in Norway are reported. The birth weights were 1,090 and 1,490 gm., respectively. They were treated in an incubator with 50% oxygen.

WALLGREN, Stockholm, Sweden.

Newborn

CAUSES OF FETAL AND NEONATAL DEATH WITH SPECIAL REFERENCE TO PULMONARY AND INFLAMMATORY LESIONS. J. B. AREY and J. DENT, J. Pediat. **42**:1 (Jan.) 1953.

The second and final installment of this paper was published, under the same title, in the *Journal of Pediatrics* **42**:205 (Feb.) 1953.

Fetal and neonatal deaths account for more than 150,000 deaths per year in the United States, or more than two-thirds the numbers of deaths attributed to cancer. In this report, Arey and Dent found an adequate anatomic cause of death in 107 of 137 fetuses and infants who died during the neonatal period. They were, in order of occurrence, (1) intrauterine anoxia, (2) intrapulmonary hyaline membranes, (3) major congenital anomalies, (4) intraventricular hemorrhage, (5) bronchopneumonia, (6) congenital syphilis, (7) intracranial trauma, as manifested by tears of the dural septa with or without subdural hemorrhage, and (8) kernicterus.

Inflammatory lesions, many of which were probably infectious in origin, played an important role as primary and contributory causes of death; they were present in 52% of the liveborn infants in this series.

The authors make a special plea for cooperation between clinicians and pathologists in the evaluation of the causes of fetal and neonatal deaths.

MACDONALD, Pittsburgh.

THE EXCHANGE OF THE RESPIRATORY GASES IN THE PLACENTA. DONALD H. BARRON, Études néo-natal. **1**:3 (Sept.) 1952.

Having in mind the differences in the oxygen pressure on the two sides of the syndesmochorial and hemochorial placenta, one might expect, because of the greater ease with which carbon dioxide moves, that CO_2 pressures would be nearly equivalent on both sides of the placenta, but aside from the suggestion to that effect in some of Keys's (1934) data, in which the comparison was made with the blood in the jugular vein rather than the uterine artery, the data on the

syndesmochorial placenta do not bear out that expectation. Can it be that the experimental procedures have in all of these cases led to an increase in the carbon dioxide pressure of the fetal blood despite the rapidity with which CO_2 may be expected to move through the placental tissues? No final answer to this question can be given, but if we accept the results of the experiments, we must look elsewhere for an explanation for the higher pressures on the fetal side. In this respect there appear to be two circumstances worthy of consideration.

The first of these is the demonstration that the carbonic anhydrase activity of laked fetal red cells is always less than that characteristic of the maternal blood (Meldrum and Roughton [1933], Stevenson [1943]. Second, the liberation of carbon dioxide from the bicarbonate of the plasma requires the shift of chloride across the membrane of the fetal red cell. Very little is known about the permeability of the fetal red cell to chloride, but it may be that this membrane is more important in the regulation of the rate of CO_2 exchange in the placenta than the placental tissues themselves.

That some membrane other than the placental tissues limits the movement of carbon dioxide from the fetal to the maternal blood is suggested by Miss Young's observations that in the rabbit, where the structural barrier between the maternal and fetal bloods is a single cell layer at the end of gestation, and the bicarbonate content of the feta lplasma tends to be higher and the chloride content lower than in the maternal plasma, a relationship suggestive of a tendency in the mother.

And this brings me to a wider topic, i. e., the relationship between the CO_2 exchange across the placenta, and the regulation of the acid-base balance of the fetal blood, but it is one that is beyond the scope of this review.

FROM THE AUTHOR'S SUMMARY.

VITAMIN E (TOCOPHEROL) IN HUMAN FETUSES AND PLACENTAE. MEI YU DJU, KARL EM MASON, and LLOYD J. FILER JR., Études néo-natal. **1**:49 (Sept.) 1952.

Chemical analyses for total tocopherol were carried out on 28 fetuses and 15 placentae at a gestation age of 2 to 6 months, 2 term placentae, and 17 premature and 6 full-term infants. The observations permitted the following generalizations.

Tocopherol concentration is low in the fetus as a whole and in individual tissues and organs and shows no particular trends during the second to sixth months of gestation. In premature and full-term infants, tissue tocopherol levels are slightly higher. These data, together with total analysis of one full-term infant in which approximately 20 mg. of tocopherol was found, are in accord with other evidence that the newborn infant possesses a rather small storage of vitamin E.

Tocopherol levels in the placenta are usually two to four times higher than those of fetal tissues and yet considerably lower than those of the maternal blood. These data support the conclusion that in man, as is true of lower mammals, there is a rather limited transfer of tocopherol across the placental barrier.

During fetal life, there is a close relationship between the lipid and tocopherol content of the fetus; this may have some metabolic significance. The capacity of the adipose tissue to serve as the major storage depot for tocopherol, which is especially marked in adult man, is apparent at or before birth.

FROM THE AUTHORS' SUMMARY.

ANOXIA IN BABIES BORN AFTER THE USUAL TIME. A. MINKOWSKI, P. BIGET, S. SAINTE ANNE-DARGASSIES, and N. CAILLEBOTTE, Presse méd. **60**:1005 (July 5) 1952.

The literature for the past years has been profuse with the question of premature infants but very poor as regards infants born after the usual time and called "postmatured." There is more danger for an infant to be three weeks behind time than to be before time at birth.

Three problems concerning postmaturation are studied by the author: 1. Is there real possibility of prolonged postmaturation? 2. If postmaturation is possible, how does it affect the fetus? 3. How do postmatured children behave at birth and during the following months?

Two cases are reported as instances of sequelae and neurologic signs in babies born after term.

The practical conclusions from the present work may be summarized as follows: 1. There is a diminution in the permeability of the placenta to oxygen, which begins 15 days following the pregnancy term and which progresses as far as exposing the fetus to severe anoxia. 2. Considering the high incidence of anoxic accidents after the 15th day, it is necessary to incite delivery before this date and, in case of failure in doing this, to perform a Caesarean section as soon as possible.

FROM THE AUTHORS' SUMMARY.

Acute Contagious Diseases

COMPARISON OF THERAPEUTIC EFFICACY OF FOUR AGENTS IN PERTUSSIS. R. G. AMES, S. M. COHEN, A. E. FISCHER, J. KOHN, A. Z. MCPHERSON, J. MARLOW, J. RUTZKY, and H. E. ALEXANDER, Pediatrics **11**:323 (April) 1953.

The results of this study suggest that Hemophilus pertussis infection is usually a mild disease in all age groups if there is effective control of most secondary bacterial infections by penicillin. Not one of the four therapeutic agents studied, streptomycin, chloramphenicol, antipertussis rabbit serum, and hyperimmune human serum, was shown to bring about prompt elimination of the signs of pertussis. On the basis of duration of infection in the patients studied, however, only 30% were suitable clinical material for comparing therapeutic agents in pertussis.

The hypothesis is advanced that prompt recovery from pertussis can be anticipated only when effective therapy is instituted early in the course of the disease; the preparoxysmal stage is recommended.

While the data failed to show convincing therapeutic value of any of the four specific agents tested, they suggested some modification by each. A significant difference in degree of influence among the four treatments was not demonstrated. On the basis of toxicity, ease of administration, and cost, chloramphenicol is, for the present, the agent of choice.

In a comparison of the capacity of the four treatments to eliminate H. pertussis from the nasopharynx, rabbit antiserum was best and chloramphenicol next.

All four specific therapeutic agents showed some influence on the characteristic response in the white blood cell count.

FROM THE AUTHORS' SUMMARY.

THE THERAPEUTIC USE OF ISONIAZID IN PERTUSSIS. S. RAPISARDI and G. MIANO, Lattante **23**:1 (Jan.) 1953.

A group of seven children, 1 to 2 years old, with pertussis, were given isoniazid in daily doses of 3 to 5 mg. per kilogram of body weight. The therapeutic results were very good. There were no untoward results from the drug. None of the children developed a bronchopneumonia, a condition which had occurred in other cases in the author's experience, when other antibiotics had been used. Mention is made that Avezzu has shown that the Hemophilus pertussis reacts to the drug in vitro.

HIGGINS, Boston.

THE CURE OF A CASE OF THE WATERHOUSE-FRIDERICHSEN SYNDROME BY CORTISONE. L. LEVI, Lattante **23**:321 (May) 1953.

A 5-year-old girl with acute meningococcic septicemia and purpura (Waterhouse-Friderichsen syndrome) was treated by pencillin intramuscularly and intrathecally, oxytetracycline (Terramycin) by mouth, and cortisone intramuscularly. The blood pressure rose from 60/0 to 99/55 within four hours after the treatment was started. The dose of cortisone at first was 50 mg. three times a day for three days and then 100 mg. daily for the next three days. The child was discharged well from the hospital on the eighth day after onset.

HIGGINS, Boston.

A CASE OF POLIOMYELITIS IN A PREMATURE INFANT TWO MONTHS OLD. L. ROCCO, Lattante **23**:470 (July) 1953.

An 8-week-old baby boy, born one month premature and weighing 2,450 gm., developed fever, spinal-fluid changes, and paralysis of the right arm. The paralysis persisted until the child died of a respiratory infection some months later.

HIGGINS, Boston.

THE SCARLET FEVER PROBLEM. HEINRICH WIESENER, Deutsche med. Wchnschr. **78**:120 (Jan. 23) 1953.

Utilizing the material of an epidemic of scarlet fever in Berlin, which, after a period of three years, appears to have come to an end, certain phases are discussed. The frequency of bacterial complications justifies the treatment of scarlet fever with an adequate dosage of penicillin. When the patients are kept in two- or three-bed rooms, early penicillin treatment definitely diminishes the frequency of such complications. Under these conditions, the children can be dismissed from the hospital on the sixth or seventh day of the treatment. The admission of a new patient to a room of a patient under treatment is permissible up to the third day of treatment. The patient under treatment receives penicillin for a few more days than usual. The children are then no longer infectious after bathing, change of laundry, and disinfection of the room. It is necessary to protect the children from reinfection and superinfection. Under proper conditions, the treatment can be carried out at home. The early penicillin treatment does not increase the recurrence of the disease. A second manifestation of the disease was as frequent among patients treated with penicillin as among those not so treated.

AMBERG, Rochester, Minn.

MULTIPLE VACCINATIONS. FRIEDRICH LINNEWEH, Med. Klin. **48**:193 (Feb. 13) 1953.

Vaccinations are recommended in the following manner. In the neonatal period, BCG is given. At the age of three months, combined vaccination against diphtheria, scarlet fever, and pertussis is given, and at the age of 9 months, smallpox vaccination. At the ages of 3, 6, and 9 years, the vaccination against diphtheria, scarlet fever, and tetanus is given, and at 12 years of age, the vaccination against diphtheria, tetanus, and smallpox is repeated.

AMBERG, Rochester, Minn.

GUILLAIN-BARRÉ'S SYNDROME ASSOCIATED WITH POLIOMYELITIS IN NEWBORN. BENGT HAGBERG and GILLIS HERLITZ, Acta pædiat. **42**:179 (May) 1953.

Two cases of Guillain-Barré's syndrome in newborns with probable poliomyelitis are reported. The infants were 10 and 8 days old. Both were afebrile, had general flaccidity with tetraplegia, and initially the cerebrospinal fluid showed marked albuminocytologic dissociation. The mother of the first had typical poliomyelitis, starting on the day of delivery. This boy recovered completely. The other developed residual paralysis characteristic of poliomyelitis. A survey of the well-documented cases of poliomyelitis in infants under 2 weeks of age reveals that general flaccidity and elevated cerebrospinal protein levels seem to be the rule rather than an exception. Different possibilities for this phenomenon are discussed.

FROM THE AUTHORS' SUMMARY.

Acute Infectious Diseases

PREVENTION AND TREATMENT OF RHEUMATIC FEVER. H. WILLIAM ELGHAMMER, Illinois M. J. **104**:187 (Sept.) 1953.

The etiology of rheumatic fever still remains unknown. The relationship between hemolytic streptococcal infections and rheumatic fever appears to be established, and the reduction of such infections is associated with a decrease in incidence and recurrence of rheumatic fever. The prevention of initial as well as recurrent attacks of rheumatic fever by judicious use of antibiotics under careful supervision has proved highly successful. The value of good hygienic care and attention to the emotional needs of the patient is a big factor in recovery. Salicylates are still the drugs of choice in the treament of rheumatic fever. The use of corticotropin (ACTH) and cortisone is not encouraged as a routine measure.

FROM THE AUTHOR'S SUMMARY.

HEMOLYTIC STREPTOCOCCAL INFECTION IN CHILDHOOD. LOWELL A. RANTA, MARGARET MARONEY, and JOSEPH M. DICAPRIO, Pediatrics **12**:498 (Nov.) 1953.

This report describes a study of hemolytic streptococcal infection during the first eight years of life. Serial study of a group of babies from birth through the fourth year demonstrated that infection by the hemolytic Streptococcus was a frequent event but that the disease was unusually mild or inapparent.

Hemolytic streptococcal infection during the first four years of life in its more severe form was characterized by the lack of an acute onset, by low-grade or absent fever, by rhinorrhea, by a protracted unself-limited course, and by the occurrence of frequent suppurative complications.

Accurate etiologic diagnosis in these cases required bacteriologic study of the nasopharyngeal flora and of the purulent discharges. The administration of penicillin abruptly terminated the disease process in these cases with prompt and dramatic clinical improvement.

After the fourth year, the disease pattern changed so that progressively more of the infections were associated with an acute febrile onset, sore throat, exudative tonsillitis and pharyngitis, and, occasionally, a skin rash.

Rheumatic fever and lesser manifestations of the rheumatic state occurred following streptococcal infection in children more than 4 years of age but were never observed in younger ones.

Evidence is presented which supports but does not establish the validity of the hypothesis that the changing patterns of clinical response to hemolytic streptococci are the results of repeated infection by these organisms with an alteration in tissue reactivity, presumably on an immunologic basis.

FROM THE AUTHORS' SUMMARY.

LIVER CHANGES IN KWASHIORKOR. S. SRIRAMACHARI and V. RAMALINGASWAMI, Indian J. Pediat. **20**:1 (Jan.) 1953.

The cardinal finding in the liver in kwashiorkor is fatty infiltration, which is marked. However, other less prominent changes are present. They include marked increase in cholesterol, displacement of glycogen and ribonucleoprotein by fat, increase in alkaline phosphatase in the liver cells, and diffuse hepatic fibrosis.

McGUIGAN, Evanston, Ill.

AN OUTBREAK OF AEROBACTER AEROGENES INFECTION IN PREMATURE AND NEWBORN INFANTS. S. OCKO-CETKOVIC and J. VESENJAK-ZMIJANAC, Ann. pædiat. **181**:17 (July) 1953.

An outbreak of Aerobacter aerogenes infection which occurred in two wards of the children's department, affecting five premature and three full-term newborn infants, is described.

In the one group of four infants, the clinical picture of the illness was that of a septicemia. In the other, only the respiratory system was involved, with two fatal bronchopneumonia cases.

Aerobacter aerogenes was proved to be the causative agent by its isolation from the throat swabs of all affected infants, from the bronchopneumonic foci in fatal cases, and from the urine and feces in some cases of septicemia.

In the therapy, only chlortetracycline (Aureomycin) proved effective. The same was confirmed in vitro. The source of infection could not be established.

FROM THE AUTHORS' SUMMARY.

THREE CASES OF CHILDREN INFECTED BY CANDIDA ALBICANS. G. CAFFARENA and P. DURAND, Gior. mal. infett. e parassit. **5**:57, (Jan.) 1953.

Three cases of extensive monilial infections in children, involving the skin, mucous membranes, and lungs, are reported. The two younger children, 15 months and 2½ years of age, died after a prolonged hospital stay and in spite of numerous types of therapy, including antibiotics, sulfonamides, iodides, and dyes. The pulmonary symptoms were mostly asthmatic; hilar gland enlargement was confirmed by x-ray pictures. The prognosis for cure in these extensive monilial infections is poor. Monilial infections have seemed to have become more frequent with the advent of antibiotic therapy.

HIGGINS, Boston.

A CASE OF MALTA FEVER ASSOCIATED WITH BANG'S DISEASE TREATED WITH CHLORTETRACYCLINE (AUREOMYCIN). A. MONTERO RODRIGUEZ, Acta pediat. españ. **11**:233 (Feb.) 1953.

The clinical history of a boy 8 years old, who had a persistent fever and gave a serum agglutination of 1:500 for Malta fever and 1:200 for Bang's disease, is here outlined.

Both brucellosis infections responded to chlortetracycline (Aureomycin). Supportive treatment of liver extracts and vitamins was given.

The fever disappeared quickly, as did the excessive sweating, and the appetite increased rapidly after treatment with chlortetracycline.

ALLEN, Santa Fe, N. M.

A CLINICAL SYMPTOM OF PFEIFFER'S GLANDULAR FEVER. GEBBARD REWERTS, Med. Klin. **48**:1473 (Oct. 2) 1953.

In a couple of cases of infectious mononucleosis, one in a boy 14 years of age, changes in the aspect of the tonsils were seen. Immediately following an initial follicular tonsillitis from the surface of the highly reddened and swollen tonsils, gray yellowish elevations arose to about 1½ and 2 mm., like palisades, which disappeared shortly, giving way to an appearance as in Vincent's angina or diphtheria. It is described as palisade symptom calling for further investigation.

AMBERG, Rochester, Minn.

Chronic Infectious Diseases

AN EPIDEMIOLOGICAL INVESTIGATION OF TUBERCULOUS MENINGITIS. J. N. COETZEE, South African M. J. **27**:441 (May 23) 1953.

Two hundred two cases of tuberculous meningitis occurring in the western provinces of the Cape of Good Hope were investigated. In 200 of these cases the organism was isolated by cultural methods. Of these 200 organisms isolated, 198 were human and 2 were bovine.

One hundred sixty-four of the patients were Negroes, 17 were natives, 16 were European, and 3 were Asiatics. Fifty per cent of the cases were under 2 years of age. In 88% of the cases of meningitis investigated, prolonged contact with a case of pulmonary tuberculosis was traced.

This study showed that ingestion of infected milk is of only slight consequence as a cause of the disease and that human pulmonary tuberculosis is the important epidemiological factor.

McGUIGAN, Evanston, Ill.

ISONIAZID IN PULMONARY TUBERCULOSIS. E. FILLA and D. SAVASTANO, Minerva pediat. **5**:86 (Feb. 15) 1953.

Fifteen children and adolescents with primary pulmonary tuberculosis were treated with isoniazid in doses averaging 5 to 6 mg. per kilogram of body weight daily. The cases were of various types, including epituberculosis, involvement of the hilum glands, miliary, and phthisis with a cavity. Excellent clinical and radiological results were obtained.

In adults with fibrous lesions, the drug was found to clear up any acute lesions but led to no change in the chronic fibrosis.

HIGGINS, Boston.

A TUBERCULOUS PROCESS IN THE AZYGOS LOBE. M. MALASPINA and F. C. GAMALERO, Minerva pediat. **5**:233 (April 15) 1953.

Stratigraphy revealed in a 6-year-old girl with tuberculous hilum lymphadenitis a density of the azygos lobe of the lung. It was quite likely there was a partial stenosis of the bronchus leading to the lobe. The process had resolved after the child had been treated with streptomycin for two months.

HIGGINS, Boston.

THE VARIATIONS IN THE CONCENTRATION OF PARAAMINOSALICYLIC ACID IN THE BLOOD AND SPINAL FLUID OF CHILDREN WITH TUBERCULOUS MENINGITIS. U. VIGNOLO-LUTATI and P. C. GAMALERO, Minerva pediat. **5**:241 (April 15) 1953.

When sodium paraaminosalicylate was given by mouth, the passage of the drug from the blood to the spinal fluid was found to be less during convalescence than during the more acute phases of tuberculous meningitis.

HIGGINS, Boston.

TUBERCULOUS MENINGITIS OCCURRING DURING SUCCESSFUL TREATMENT OF TUBERCULOUS PERICARDITIS BY STREPTOMYCIN. ACETO GIACOMO, Minerva pediat. **5**:257 (April 15) 1953.

An 8-year-old boy had a limp as a result of a tuberculous hip six years previously. The present acute illness was a pericarditis with effusion. Over a three-day period, 360 cc. of fluid was removed and 0.30 gm. of dihydrostreptomycin injected on pericardial taps. Tubercle bacilli were found in the fluid. Daily streptomycin injections were given intramuscularly, and the x-ray shadow showed that the heart was approaching normal size. On the 13th day after the first tap, the patient developed tuberculous meningitis; he died four days later.

HIGGINS, Boston.

THE THERAPEUTIC ACTION OF ISONIAZID ON CHILDHOOD TUBERCULOSIS. A. ROSINI, A. FATTORI and S. GABALLO, Minerva pediat. **5**:703 (Aug. 31) 1953.

The results are presented of the treatment of 81 tuberculous children in a sanatorium with isoniazid. Of 66 children with the allergic exudative reaction, 48 showed improvement, 12 showed no change, and 6 became worse. It was apparent that the drug, in causing lysis of the tubercle bacilli, may on occasions aggravate markedly the allergic reaction.

Of 14 children with primary lesions wthout the allergic exudate reaction, 7 showed improvement and 7, no change. It appeared that, when the treatment was started early in these latter cases, the results with isoniazid were excellent.

HIGGINS, Boston.

A CLINICAL EVALUATION OF THE EFFECT OF ISONIAZID ON CHILDREN WITH TUBERCULOSIS. T. PERI and G. CRAVOS, Minerva pediat. **5**:826 (Sept. 30) 1953.

Fifty-eight children in Trieste were treated for tuberculosis with isoniazid. The drug proved more efficacious in lesions of the exudative pulmonary type than in lesions of the hilar glands. The best results were obtained when the drug was given along with streptomycin and para-aminosalicylic acid. No toxic effects from the drug were encountered.

HIGGINS, Boston.

A CHILD WITH DIFFUSE TUBERCULOSIS, PREVIOUSLY ERRONEOUSLY DIAGNOSED AS NON-LIPOID RETICULOENDOTHELIOSIS. F. PARINI and P. M. SCARIZZA, Pediatria **61**:249 (March) 1953.

A 3-month-old child had marked malnutrition, very large spleen and liver, enlarged lymph nodes, nodular infiltration in the lungs, and encephalopathies. A diagnosis of nonlipoid reticulo-endotheliosis was made.

Autopsy findings revealed a diffuse tuberculous infection. The Mantoux tests had been negative.

HIGGINS, Boston.

CLINICAL STUDY IN THE COMPARISON OF THE USE OF STREPTOMYCIN AND ISONIAZID IN THE TREATMENT OF TUBERCULOUS MENINGITIS. M. VIZUETE, Arch. pediat. Barcelona **4**:65 (July-Aug.) 1953.

This is a schematic comparison of the clinical effects when streptomycin is used and when isoniazid is used.

At the present, the latter gives much better results with none of the irreversible changes in nervous tissue found with prolonged treatment.

The percentages of cures with streptomycin was 40%, whereas it was 83% in the case of isoniazid. Hospital stay was cut in half in the cases studied.

ALLEN, Santa Fe, N. M.

SYMPTOMATOLOGY OF BEGINNING MENINGITIS TUBERCULOSA IN CHILDREN. MARIANNE GROLL-KAHL, Med. Klin. **48**:554 (April 17) 1953.

Of 362 cases of tuberculous meningitis, 244 started gradually, 188 acutely. The early symptoms of those with more gradual onset are discussed and compared with those of acute onset.

AMBERG, Rochester, Minn.

IMPROVEMENT OF TREATMENT OF TUBERCULOUS MENINGITIS WITH ISONIAZID. H. U. KOTTGEN and K. HARTUNG, Med. Klin. **48**:1624 (Oct. 30) 1953.

The combination of streptomycin with isoniazid treament in cases of tuberculous meningitis is recommended. Streptomycin is administered intraspinally and isoniazid, in most cases, in the suboccipital space. The injection of each is given every second day.

AMBERG, Rochester, Minn.

ANATOMICAL PATHOLOGY IN TUBERCULOUS MENINGITIS IN CHILDREN TREATED WITH STREPTOMYCIN. II. A. DE MINJER, Maandschr. kindergeneesk **21**:213 (July) 1953.

The clinical course of tuberculous meningitis in 10 children was not markedly influenced by treatment with streptomycin, although the antibiotic was given intramuscularly and intrathecally in adequate dosage. There were seven cases of subprimary meningitis with severe primary tuberculosis of the lung and lymph nodes. Nearly all these cases showed at the same time an extensive hematogenous generalization.The prognosis of tuberculous meningitis is influenced unfavorably by such a generalization, as is shown by the observation of two children who were infected shortly after birth and died of severe primary tuberculosis with extensive generalization. At autopsy, both cases revealed an incipient tuberculous meningitis, which had not yet given rise to clinical symtoms. In these cases, death was considered to be due to the primary tuberculosis and the generalization before the meningitis had had the opportunity to develop. It is probable that in one of these children treatment with streptomycin for some weeks had delayed the progress of the meningitis.

In three cases, the meningitis developed a considerable time after the primary infection. None of these cases showed any hematogenous generalization.

The extension of the meningitis at the base of the brain was different in our cases. There was no direct relation between this extension and the duration of the illness, but severe extension was generally observed when treatment was started late in the course of the disease. It is probable that in these cases the lesions of the meninges were already too severe to be influenced by the treatment. However, treatment still presumably delayed the course of the disease in these cases, so that the meningitis was still able to develop to some extent.

The age of the patients and the lapse of time between the primary infection and the beginning of the meningitis were also important. The most severe extension was observed in young children with extensive generalization and meningitis that developed immediately after the primary infection. If treatment was started early in these cases, we found at autopsy a less extensive meningitis at the base of the brain, even when the duration of the disease had been prolonged.

The prolongation of the clinical course was most marked in older children, especially in those with postprimary meningitis without hematogenous generalization. In those cases we again observed an extensive meningitis, but the character of the tuberculous inflammation had altered. In young children who had only a short course of treatment, the meningitis showed a predominantly exudative tuberculous inflammation. In young children, we found more extensive caseation, but there was also some proliferative reaction. More fully treated cases showed a rather extensive development of tuberculous granulation tissue. Moreover, it is probable that in older children, especially in those with postprimary meningitis, the tuberculous inflammation is already naturally inclined to more proliferative reaction than in young children with subprimary meningitis.

Evidence of healing, consisting of beginning organization of exudate or encapsulation of caseous foci, was found in one case only.

The brain tissue in the neighborhood of the tuberculous inflammation was markedly altered in all cases. The changes consisted of perivascular extensions of the tuberculous inflammation, edema and infiltration with inflammatory cells, degeneration of ganglion cells, and proliferation of glia cells. Moreover, some cases showed areas of softening. The involvement of the brain parenchyma was less severe in well-treated cases, but all cases showed advanced lesions in the depth of the sulci, presumably because streptomycin does not penetrate sufficiently in these areas. Inadequately treated cases with exudative tuberculous inflammation of the meninges showed

typical arteritis. In more advanced cases, the arteries were narrowed or even completely occluded by proliferation of the intima. The softening of the brain tissue in many cases was ascribed to the vascular lesions.

In all cases, the ventricular lining showed granular ependymitis, especially in cases with subprimary meningitis. In cases with well-developed tuberculous granular tissue in the meninges, the lesion had the structure of tubercles. The other cases showed only inflammatory cells and proliferation of glia cells.

The ventricles were dilated in nearly all cases. The dilatation was asymmetrical in some. The hydrocephalus was presumably caused not only by mechanical obstruction, but general changes of the brain matter probably also played a role. It is considered that in some cases the brain parenchyma was altered, so that dilatation of the ventricles developed even when the intraventricular pressure was normal or only slightly increased.

We have the impression that severe involvement of the brain tissue adjacent to the tubeculous lesions in the meninges had led clinically to coma early in the course of the disease. Most of the cases with marked hydrocephalus had shown severe decerebration rigidity, presumably caused by the same general alteration of the brain matter that also favored the development of the hydrocephalus.

In one case the inflammation of the meninges had a purulent character, caused by secondary infection shortly before death.

Only one case showed a macroscopically visible tuberculous lesion in the brain which was not a direct extension of the tuberculous inflammation of the meninges.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

HOMOZYGOUS TYPE "C" HEMOGLOBIN. THEODORE H. SPAET, ROBERT H. ALWAY, and GAYLORD WARD, Pediatrics **12**:483 (Nov.) 1953.

A case of "homozygous" Type "C" hemoglobin is reported in a Negro child. Although the patient was clinically free of hemolytic disease, the peripheral blood showed numerous target cells, and a compensated hemolytic process was demonstrated. Clinical and theoretic implications of the condition are discussed.

FROM THE AUTHORS' SUMMARY.

CLOT DENSITY METHOD OF FIBRINOGEN DETERMINATION IN SOME PEDIATRIC CONDITIONS. ABRAM KANOF, SAMUEL LOSNER, and BRUNO W. VOLK, Pediatrics **12**:564 (Nov.) 1953.

The clot density, a method of rapid fibrinogen determination, was studied serially in a group of children and compared simultaneously with the corrected sedimentation rate.

In normal children, the clot density showed no deviation from the normal levels, which range from 5 to 15, while the sedimentation rate displayed many erratic fluctuations.

In such conditions as upper and lower respiratory infections or urinary tract infections, the clot density rose slightly and subsided promptly under therapy, while the sedimentation rate frequently showed maximum elevations.

In acute rheumatic disease, there was constant and close correlation between the degree of clinical manifestations and the clot density. The sedimentation rate, however, frequently did not correspond with the intensity of the inflammatory process.

In rheumatic children treated with cortisone, the clot density is the first indication of a therapeutic effect. Moreover, with the cessation of cortisone administration and the worsening of clinical symptoms, as well as laboratory data, the decline of the clot density is the first indication of a "rebound," rather than an exacerbation.

The clot density may be an aid in the differentiation of fever of central origin.

Cortisone seems to be devoid of a direct nonspecific effect upon the fibrinogen concentration.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat, and Ear

MODERN CONCEPTS IN THE TREATMENT OF OTITIS MEDIA. BERNARD ZONDERMAN, New England J. Med. **249**:643 (Oct. 15) 1953.

The author discusses the treatment of otitis media from four viewpoints, the use and abuse of antibiotics, the importance of myringotomy, the significance of serous otitis media, and the problem of recurrences.

He points out that failures in the initial chemotherapy of otitis media are increasing, as well as the incidence of deafness and mastoiditis. The need for anatomic and physiologic knowledge of the hearing apparatus is greater in this antibiotic era, rather than less. It is emphasized by illustrative cases that the prevention of otitic complications and of chronic draining middle-ear infection is best accomplished by myringotomy early in acute suppurative otitis media and long-term, complete, and carefully observed antibiotic therapy.

Secretory nonpurulent otitis media is discussed in the light of its role in deafness, diagnosis, and proper definitive treatment.

Lastly, the problem of recurrent otitis media is discussed. Causes and various treatments of this condition are enumerated, and a description of adenoidectomy under direct inspection is given.

The author lends his support to those who condemn the use of throat lozenges and troches which contain insignificant amounts of antibiotic agents.

WHEELOCK, Denver.

AN INVESTIGATION OF THE SPONTANEOUS SPEECH SOUNDS OF FIVE-YEAR-OLD DEAF-BORN CHILDREN. JOSEPHINE CARR, J. Speech & Hearing Disorders **18**:22 (March) 1953.

Phonetic transcription was made of the spontaneous speech of 27 congenitally deaf boys and 21 congenitally deaf girls, all 5 years of age. Girls used more vowel types and used them with more frequency than did boys and in a manner and degree like hearing infants of 11 to 12 months of age. All used from 7 to 20 consonant types during 90 breath units. Girls used a narrower but slightly more frequent range of consonant types than did boys. All used many spontaneous speech sounds. These were natural in quality and uttered in a manner free from strain and selfconsciousness. Such spontaneous speech sounds should be accepted and encouraged by teachers of the deaf.

PALMER, Wichita, Kan.

Diseases of Lungs, Pleura, and Mediastinum

INDETERMINATE PULMONARY LESIONS. WILLIAM E. ADAMS, Illinois M. J. **104**:205 (Sept.) 1953.

Indeterminate pulmonary lesions are classified as those which resist identification when all means of investigation are utilized. They may be neoplastic, inflammatory, or congenital in origin. The symptomatology of such lesions may vary considerably.

Most primary neoplastic lesions of the lung are of the malignant type. A larger percentage of the peripheral lung tumors are of the squamous-cell type, some of which are slow-growing. Metastases may be absent after many months. Adenocarcinoma of the lung metastasizes earlier; symptoms due to the metastases are not infrequently the first caused by the tumor.

Circumscribed tuberculous lesions are not infrequently impossible to identify, except by cultures and guinea-pig innoculation from a surgical specimen.

Congenital lesions may be of the pulmonary or vascular type. A history of an insidious onset of a pulmonary suppurative process in a child without the usual etiologic factor for the production of bronchiectasis or lung abscess should suggest the possibility of congenital malformation of the lung. Bronchoscopic examination and x-rays following iodized-oil injection are usually not diagnostic. In such cases, when the patient's condition warrants it and a thorough preparation for operation has been made, exploration and resection of the involved portion is indicated, according to Adams. Vascular malformations within the lung produce symptoms less frequently than pulmonary anomalies and are thus less frequently identified.

Adams points out that if the benefit of early exploration in patients with indeterminate pulmonary lesions is kept in mind, the outlook for pulmonary malignancy will be much enhanced.

BARBOUR, Peoria, Ill.

CLINICAL EVALUATION OF A NEW ANTITUSSIVE AGENT. SAMUEL HYMAN and SAMUEL H. ROSENBLUM, Illinois M. J. **104**:257 (Oct.) 1953.

A codeine derivative, dihydrocodeinone (Hycodan), has been clinically tested for relief of cough according to specified criteria. The optimum dose was established in a pilot study. Results indicate it is an effective and satisfactory antitussive agent which relieves cough without interference with expectoration and without other apparent undesirable side reactions.

FROM THE AUTHORS' SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

DIAPHRAGMATIC HERNIA. GEORGE D. LAVERS and CHARLES D. BRANCH, Illinois M. J. **104**:193 (Sept.) 1953.

Diaphragmatic hernia is being recognized more frequently and is not as rare as one thought. In five years, 103 cases were seen in St. Francis Hospital. The clinical diagnosis is still not made often enough. Analysis of these cases discloses a group of symptoms which, when present, should suggest the diagnosis of diaphragmatic hernia. The esophageal hiatus type seen in elderly persons is the most common. The treatment is outlined.

FROM THE AUTHORS' SUMMARY.

LYMPHOID HYPERPLASIA OF THE APPENDIX. ALFRED A. NATHANS, HYMAN MERNESTEIN, and SAMUEL S. BROWN, Pediatrics **12**:516 (Nov.) 1953.

One hundred ninety-eight cases of lymphoid hyperplasia of the appendix, some of which had other associated pathology, have been analyzed.

Comparison has been made with an analogous series of acute appendicitis in children.

There is no precise differential diagnosis between acute appendicitis and lymphoid hyperplasia of the appendix. Each case has to be watched carefully, and any increase in local signs is an indication for surgery.

Lymphoid hyperplasia is frequently the precursor of acute appendicitis.

FROM THE AUTHORS' SUMMARY.

PSEUDOCHOLEDOCHAL CYST. ARTHUR G. SMITH and SAM F. SEELEY, Pediatrics **12**:536 (Nov.) 1953.

A case of a fibrous-walled bile-containing cyst in an infant, secondary to injury to the common duct, is presented. Since this is believed to be the first such case to appear in the medical literature, the term pseudocholedochal cyst is suggested. A brief review of the clinical picture of choledochal cyst is given, since the findings in this case and in the reported cases of true choledochal cysts are quite similar.

FROM THE AUTHORS' SUMMARY.

DEVELOPMENTAL ABNORMALITIES OF THE DUODENUM PRODUCING OBSTRUCTION. RICHARD F. MCCLURE and ELMER F. WAHBY, Radiology **61**:516, 1953.

A classification of congenital obstructing lesions of the duodenum is presented, and the development of each type is briefly described. One newborn female had a segment of atresia 8 mm. long proximal to the ampulla of Vater. A premature female had a tightly stretched band across the duodenum from the gall bladder to the colon and another band at the duodenojejunal junction. Two other newborn infants showed bands compressing the third and fourth portions of the duodenum, respectively. The common congenital obstructing lesions are atresia, stenosis, and cholecystodenocolic membranes.

The roentgenographic deformity is illustrated in four infants and in a 23-year-old adult.

ANSPACH, Riverside, Ill.

FUNCTIONS OF INTESTINAL FLORA: THE INTERFERENCE CAUSED BY ANTIBIOTICS. J. C. VALL BONERES, Arch. pediat., Barcelona **4**:1 (July-Aug.) 1953.

The author discusses the composition and distribution of intestinal flora, also the difference at various ages. The function of intestinal flora in the utilization of vitamins, their function in converting lactose to lactic acid, the part played by these bacteria in the glycogen storage in the liver, and, lastly, the secretion of enzymes of a protective nature and the maintenance of a symbiosis are explained.

The careful use of antibiotics does not affect these functions too seriously, but prolongation of their use may leave the intestine as devoid of flora as the meconium in a newborn baby.

ALLEN, Santa Fe, N. Mex.

APPENDICITIS IN INFANTS AND YOUNG CHILDREN. HANS-JOACHIM WISSFELD, Deutsche med. Wchnschr. **78**:1502 (Oct. 30) 1953.

Appendicitis in infants and early childhood is rather infrequent. In a period of two years, 1,178 appendectomies were performed. Of these, nine occurred in infants and children under 3 years of age and twelve during the ages of 3 to 5 years.

AMBERG, Rochester, Minn.

PULMONARY ASPIRATION IN PYLOROSPASM. LOTHAR SEELIG, Monatsschr. Kinderh. **101**:313 (June) 1953.

In contrast to the prevailing belief that infants with pylorospasm do not aspirate, the author found aspiration into the lungs in 19 cases on serial x-ray films. These consisted of mediastinal pleurisy and tracheobronchial lymphadenitis. No clinical findings of aspiration were noted in these patients.

HARTENSTEIN, Syracuse, N. Y.

Diseases of Genitourinary Tract

CHRONIC URINARY TRACT INFECTION IN A FEMALE CHILD. WILBUR G. LAWSON, J. Pediat. **43**:263 (Sept.) 1953.

Lawson reports a case of a 5-year-old girl with intractable enuresis thought to be related to a chronic low-grade vaginitis not caused by the gonococcus. The vaginitis was treated with local suppositories of diethylstilbestrol, with prompt relief of vaginal symptoms and subsequent disappearance of urinary symptoms. The patient was treated over a period of six weeks. One year after treatment was stopped, she was still free of symptoms.

MACDONALD, Pittsburgh.

PSEUDOPRECOCIOUS PUBERTY IN GIRLS AS A RESULT OF ESTROGEN INGESTION. CHARLES D. COOK, JANET W. MCARTHUR, and WILLIAM BERENBERG, New England J. Med. **248**:671 (April 16) 1953.

The authors describe two girls, aged 4 and 7, with breast enlargement and dark pigmentation of the areolae, nipples, and linea alba associated with vaginal bleeding. Since estrogenic substances are known to produce this abnormal pigmentation when ingested, inhaled, or absorbed through the skin, investigation in this direction was begun.

Routine studies were performed, as well as examination of vaginal smears for cornified epithelial cells and pH changes. Urinary gonadotropin levels were determined and found to be increased in one case and decreased in the other. The implications of these data are discussed.

The occurrence of regression in the vaginal smear over a two- to four-week period suggested that a policy of withholding surgical exploration in cases of suspected medicational precocious puberty is a valid one. This applies solely to instances wherein pelvic examination is entirely negative or equivocal.

WHEELOCK, Denver, Colo.

THE PROBLEM OF RENAL HYPERTENSION. RUDOLF MATZNER, Monatsschr. Kinderh. **101**:479 (Nov.) 1953.

Two months after rupture of the right kidney due to a fall from a tree, an 11-year-old boy suddenly became unconscious, manifested a hypertension of 210/180, and had multiple small intracerebral hemorrhages, as proved by electroencephalogram, ventriculography, and cerebral arteriography. Right nephrectomy restored full consciousness, and the patient became normotensive and asymptomatic. His blood pressure had remained normal (110/80) one and one-half years later.

HARTENSTEIN, Syracuse, N. Y.

Diseases of Ductless Glands; Endocrinology

PEDIATRIC ENDOCRINOLOGY: NOTES ON SOME RECENT ADVANCES. FRANK L. PLACHTE, California Med. **79**:353 (Nov.) 1953.

Until recently, congenital adrenocortical hyperplasia has defied most medical and surgical therapeutic efforts. However, in properly selected patients, cortisone will suppress the abnormal cortical hormone production. This, in turn, will lead to previously inhibited maturation and developmental progress.

Adrenocortical insufficiency calls for much diagnostic alertness, as early recognition and immediate treatment are of paramount importance. The available therapeutic means are beneficial, although their limitations and potential dangers should be heeded.

Among newly developed diagnostic techniques, thyrograms promise to be helpful in the study of thyroid hyperplasia and neoplasia. Thyroid cancer, occurring infrequently in childhood, should at the earliest possible time be treated surgically and with postoperative radiation therapy.

PRYOR, Redwood City, Calif.

EFFECT OF LYOPHILIZED THYMIC EXTRACTS ON SERUM CALCIUM AND PHOSPHORUS. H. SCHWARTZ, M. PRICE, and C. A. ODELL, Metabolism **2**:261 (May) 1953.

The authors report a series of interesting observations which have a bearing on a relation between metabolism of calcium and phosphorus and the activity of the thymus gland. They had noted previously that in patients suffering from myasthenia gravis there was frequently an elevation of the concentration of inorganic phosphorus in the serum. The hyperphosphatemia was not associated with any variation from the normal in the concentration of calcium or phosphatase activity in the serum.

In order to investigate the possibility that the alteration in concentration of phosphorus was in some way associated with an enlargement of the thymus, the authors made aqueous extracts of calf thymus and injected these into experimental subjects and animals. Following these injections into normal humans, patients with myasthenia gravis, and dogs, there occurred in most instances a sharp rise in the concentrations of serum calcium and phosphorus, which reached a maximum within 3 hours and returned to normal levels within 24 hours. In one normal human, the concentration of calcium increased from 9.4 to 15.2 mg. per 100 cc., and in another the phosphorus rose from 3.2 to 4.8 mg. per 100 cc. of serum.

KAPLAN, New York.

SUPRARENAL TUMOR AND CALCIFICATION SEEN IN A SIMPLE ROENTGENOGRAM. MANUEL SUAREZ, Rev. españ. pediat. **9**:889 (Sept.-Oct.) 1953.

The author presents the case of a child, seen in 1936, with a malignant tumor which on a flat plate showed calcification. He had kept the clinical record and pictures of the child, and he reviews these in the light of more recent knowledge.

The child had a marked macrosomia, was retarded mentally, and showed marked masculine hirsutism. She died suddenly because of suprarenal insufficiency.

ALLEN, Santa Fe, N. M.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

CONGENITAL FIBROMYXOSARCOMA OF THE OS CALCIS. JOHN J. SLAVENS, Pediatrics **11**:617 (June) 1953.

A case of congenital fibromyxosarcoma involving the os calcis, successfully treated by amputation, is reported. The rare occurrence of bone tumors in the newborn period is noted, and a brief review of cases reported in the literature is given. The nature of these tumors, which are of relatively low malignancy, is discussed. Early diagnosis by roentgen examination and biopsy study, followed by prompt effective surgical treatment, offer the best chance for a successful outcome.

FROM THE AUTHOR'S SUMMARY.

A CASE OF MYATONIA CONGENITA. P. MARTINELLI, Lattante **23**:26 (Jan.) 1953.

A baby girl 3 months of age, whose parents were first cousins, had had weakness of all muscles since birth. The creatine and creatinine content of the blood serum was found to be above normal. A diagnosis of Oppenheim's myatonia congenita was made.

HIGGINS, Boston.

THERAPY OF ACUTE HEMATOGENOUS OSTEOMYELITIS IN CHILDHOOD. GUSTAV NUHSBAUMER, Wien. klin. Wchnschr. **65**:146 (Feb. 13) 1953.

The first step in the treatment of acute osteomyelitis is the elimination of the general infection by penicillin. When this treatment does not clear up the osteomyelitis, which happened in 20 of 45 cases, surgical intervention is indicated.

AMBERG, Rochester, Minn.

ACUTE HEMATOGENOUS OSTEOMYELITIS. H. W. TEN CATE, Maandschr. kindergeneesk. **21**:411 (Dec.) 1953.

After a discussion of the pathogenesis of acute hematogenous osteomyelitis, a survey of postwar literature on the treatment is given, with special reference to the question of surgical intervention. It is concluded that the best results may be obtained by antibiotic treatment, which may be supported if necessary by conservative surgery.

FROM THE AUTHOR'S SUMMARY.

Diseases of Eye

THE MANAGEMENT OF STRABISMUS. ARTHUR JAMPOLSKY, California Med. **79**:367 (Nov.) 1953.

The original causes of strabismus and the complications that develop from efforts by a child to adjust to the condition may present a complex diagnostic and therapeutic problem. The complications of suppression, amblyopia, contractures, and anomalous visual habits may become more difficult to correct than the cause of the strabismus. The longer the duration of strabismus, the more complex the problem, the more difficult the treatment, and the less the probability of functional cure. Treatment should be started early. Correction may be brought about by the use of glasses, eye patches, and orthoptic training, or by operation. If anatomic abnormality prevents bringing the eyes into line by conservative means, operation should be carried out after the best results possible by these means have been achieved. Surgical treatment, too, where it is indicated, should be done early, in order that normal binocular cooperation can develop before abnormal visual habits can become established.

PRYOR, Redwood City, Calif.

PRELIMINARY REPORT OF A NEW METHOD FOR THE EXAMINATION OF NYSTAGMUS THROUGH TELEVISION. JOSEPH A. SULLIVAN, WALTER H. JOHNSON, and W. E. HODGES, Laryngoscope **63**:1193 (Dec.) 1953.

Nystagmus was photographed by a television camera. The image was enlarged and transmitted to a television screen. A large image such as this can easily be observed, measured, and, if so desired, photographed.

HITSCHLER, Philadelphia. [A. M. A. ARCH. OTOLARYNG.].

DEVELOPMENT OF VISION AND ITS RELATION TO MUSCLE ANOMALIES. GEORGE S. ELLIS and RICHEY L. WAUGH JR., South. M. J. **46**:363 (April) 1953.

The development of vision is a continuous process which involves learning and practice. The development of fixation and of acuity proceed simultaneously. The development of fusion ultimately gives stable binocular vision. An acuity of 20/2000 at 5 months of age improves to about 20/45 at 2 years. A fusion reflex is evident at 2 years of age. Normal binocular vision is usually present by the sixth year. Strabismus may result from an inability to use the visual apparatus correctly or from faulty development of the fusion reflex. It may lead to amblyopia ex anopsia. Treatment of strabismus should be started sufficiently early so that binocular vision can be restored.

LOGAN, Rochester, Minn.

Cutaneous Diseases; Allergy

LYMPHOBLASTOMAS IN CHILDHOOD: CUTANEOUS MANIFESTATIONS. LAWRENCE M. NELSON, California Med. **78**:208 (March) 1953.

The lymphoblastomas occurring in childhood are divided for purposes of discussion into lymphocytoma cutis, mycosis fungoides, lymphosarcoma, Hodgkin's disease, and leukemia. The cutaneous lesions may be either specific (as a result of the infiltration of the skin with specific cells of the conditions) or toxic (nonspecific). With the possible exceptions of mycosis fungoides, the cutaneous manifestations are not diagnostic. The final diagnosis depends upon microscopic examination of the specific tissue involved and the coordination of the clinical and microscopic findings.

PRYOR, Redwood City, Calif.

THE CLINICAL AND HISTOLOGICAL CONSIDERATION IN TWO CASES OF PERIANAL PAPILLOMATOSIS IN TWINS. R. CORDA, Ann. ital. pediat. **6**:526 (Dec.) 1953.

The author describes a form of perianal papillomatosis in twin sisters, characterized by the identity of the morphologic aspect and the localization.

The clinical evolution and the early beginning in respect to the age of the patients are rather uncommon characteristics of that disease, and the author shows several pathogenetic possibilities as to the cause of this affection.

FROM THE AUTHOR'S SUMMARY.

Miscellaneous

PRACTICAL APPLICATION OF PAPER ELECTROPHORESIS. THEODORE H. SPAET, California Med. **79**:271 (Oct.) 1953.

Paper electrophoresis of proteins is a simple economical method well adapted to routine laboratory use. It can give important diagnostic information concerning serum proteins and is invaluable in the differential diagnosis of diseases in which there are abnormal hemoglobin values.

Electrophoresis on filter paper as described is a procedure well adapted to routine laboratory use. The cost is negligible, the technique can be learned by unskilled personnel in a short time, and many determinations can be run simultaneously. The information gained from electrophoretic studies of the serum proteins exceeds that obtained from the usual protein analyses, and the method is less laborious. It is especially adapted to pediatric needs. Since only minute amounts of blood are needed, capillary blood can be used. In the study of hemoglobin, the information provided by electrophoretic analysis cannot be duplicated by other methods.

PRYOR, Redwood City, Calif.

SEVERE DIARRHEA WITH FATAL CIRCULATORY COLLAPSE AFTER USE OF CHLORAMPHENICOL (CHLOROMYCETIN) AND OXYTETRACYCLINE (TERRAMYCIN). R. CRAMER and E. ROSSI, Helvat. paediat. acta **8**:544 (Dec.) 1953.

In five cases of children with different infectious diseases, uncontrollable diarrhea, and fatal circulatory collapse occurred after brief administration of antibiotics. In two cases, a pseudomembraneous enteritis due to Staphylococcus could be demonstrated.

This new clinical entity has often been described in adults as a complication arising from antibiotic therapy. The similarity between this and the clinical pictures after Staphylococcus food poisoning has been stressed. Hematological changes in the blood and bone marrow, particularly the agranulocytosis appearing in one case, are discussed in detail. Therapy in such cases includes, besides vigorous parenteral administration of fluids, substitution of the antibiotic by a new one, such as erythromycin, which has proved active against Staphylococcus.

FROM THE AUTHORS' SUMMARY.

HOSPITALIZATION PRACTICES FOR INFANTS IN RURAL AREAS. DEWET BARBATO, Arch. pediat. Uruguay **24**:73 (Feb.) 1953.

There is a general agreement in reporting that lack of maternal care bears a detrimental effect on the infant's personality development. In a recent book "Maternal Care and Mental Hygiene" (OMS, Geneva), Dr. Bowlby reviews the literature and research on the subject. In order to find out what practices are carried out in rural areas and in state community hospitals, as far as hospitalization of infants is concerned, 22 such hospitals were surveyed.

The result shows that even though official responsibility has been taken, the mother is allowed to room with her sick baby (aged less than 3 years) in all 22 centers; only in two of them the condition was set that the mother should breast feed her child. Facilities for the mother ranged between none at all (chair) to an extra bed next to the crib.

All 22 hospital directors were in favor of the joint hospitalization of the mother with her sick baby.

FROM THE AUTHOR'S SUMMARY.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in Des Moines, Iowa, on March 19, 20, and 21, 1954.

Anderson, Wallace Roger, Austin, Minn.
Bergan, Robert Otto, Duluth, Minn.
Booher, Craig E., Grand Rapids, Mich.
Bridge, Allyn G., Minneapolis.
Burgert, Eran Omer, Jr., Omaha.
Campbell, John Cadwell Wingfield, Great Lakes, Ill.
Carabelle, R. William, Port Arthur, Texas.
Crew, Morton R., Decatur, Ill.
Dodge, Milton, Kansas City, Mo.
Follo, Paige B., Columbus, Ga.
Griggs, Stewart L., Green Bay, Wis.
Grossman, Aaron, Winnetka, Ill.
Gwinn, John Lemuel, Rochester, Minn.
Hagan, Robert K., Chicago.
Harkness, John W., Wauwatosa, Wis.
Hart, Joseph Thomas, Portland, Ore.
Heilig, William Richard, St. Paul.
Henry, Robert L., Little Rock, Ark.
Hooker, James W., Urbana, Ill.
Howard, David Snow, San Antonio, Texas.
Jarvi, Rudolph Michael, Saginaw, Mich.
Jurow, Seymour S., Rantoul, Ill.
Knappenberger, Roy C., Wichita, Kan.
Kodl, Francis, Berwyn, Ill.
Langewisch, William H., Rockford, Ill.
Lanoff, Gilbert, Chicago.
Leach, Charles Austin, Champaign, Ill.
LeBus, Howard E., Gladewater, Texas.
Maimon, A. Currie, River Forest, Ill.
Martin, Francis Paul, San Francisco.
Mauran, William L., Jr., Providence, R. I.
Mercer, Jeanne Kehoe, Oak Park, Ill.
Middelkamp, John Neal, St. Louis.
Mitchell, Richard C., Mason City, Iowa.
Odell, James E., Iowa City.
Olson, Detlof M., Minneapolis.
Padorr, Marvin P., Chicago.
Peltier, Hubert Conrad, Mishawaka, Ind.
Price, Walter Stauffer, San Francisco.
Reed, Holley William, Amarillo, Texas.
Ruppa, Rex, Milwaukee.
Schimmelpfennig, Robert William, Marion, Ind.
Schunk, George James, Grants Pass, Ore.
Scott, John Richard, Indianapolis.
Siegel, Alan Cyril, Winnetka, Ill.
Smith, Rodney M., Pueblo, Colo.
Staub, Henry Paul, Minneapolis.
Stedelin, John A., Centralia, Ill.
Strachman, Jerome, Cheyenne, Wyo.
Suits, John James, Marshfield, Wis.
Toll, David, Greenville Air Force Base, Miss.
Tracy, Paul Critchell, Park Ridge, Ill.
Waickman, Francis Joseph, Scott Air Force Base, Ill.
Wallace, Hobart E., Fort Leonard Wood, Mo.
Webb, Edwin L., Montgomery, Ala.

Contribution from Junior League of Brooklyn to Pediatric Research Laboratory.—The Junior League of Brooklyn has given to the new Pediatric Research Laboratory at the State University of New York College of Medicine at New York City, Brooklyn, the sum of $4,000.

ANNOUNCEMENTS

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations on April 30 and May 1 and 2, 1954, in New York, and on June 25, 26, and 27, 1954, in San Francisco.

Pan American Congress of Pediatrics.—The Pan American Congress of Pediatrics will be held from July 15 to 21, 1954, at São Paulo, Brazil.

PERSONAL

Appointment for Dr. Daniel C. Darrow.—Dr. Daniel C. Darrow has accepted appointment to a newly created chair in the Department of Pediatrics at the University of Kansas School of Medicine. He will become Children's Mercy Hospital Professor of Pediatrics on July 1, 1954. Children's Mercy Hospital of Kansas City, Mo., has been affiliated with the University of Kansas School of Medicine for the purposes of undergraduate and postgraduate education for the past year. Dr. Darrow will have research facilities both at Children's Mercy Hospital and the University of Kansas Medical Center. He will assume his new duties about August 1, after delivering a series of lectures in Paris at the request of the French government.

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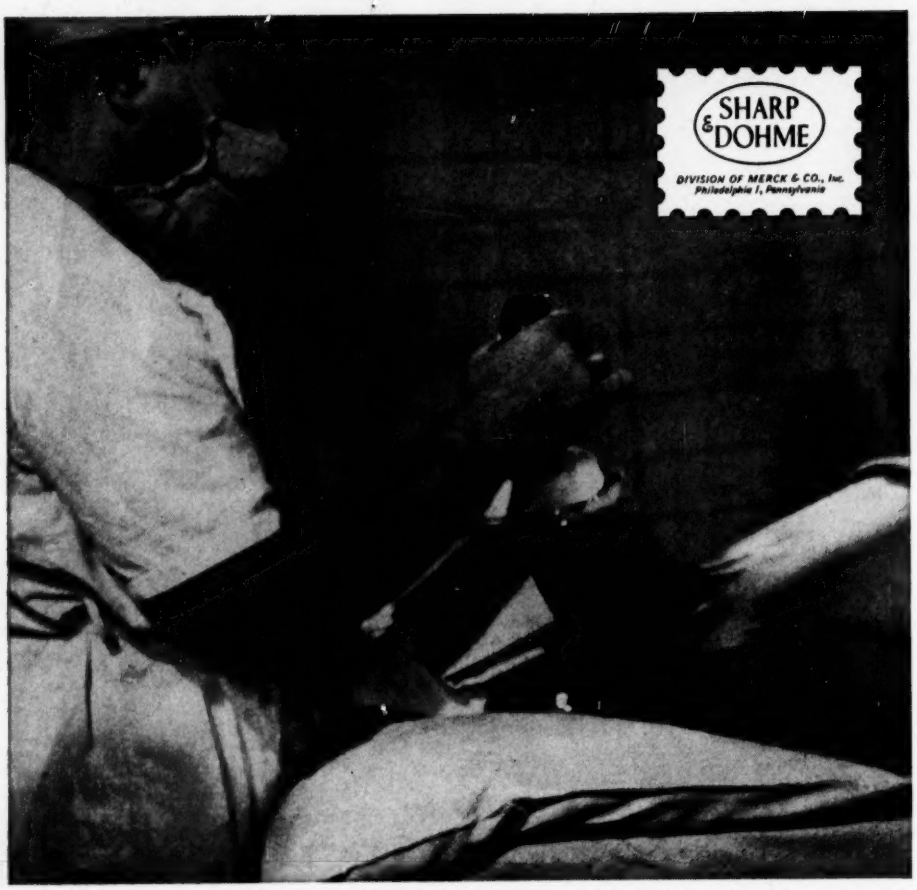

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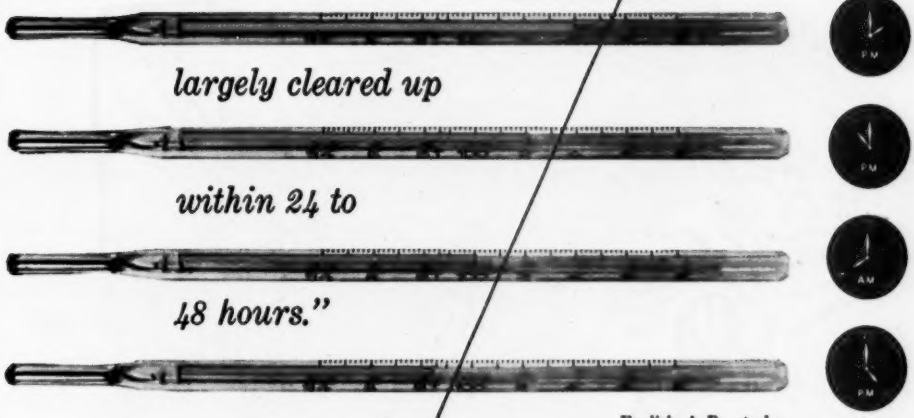

largely cleared up within 24 to 48 hours."

English, A. R., et al.:
Antibiotics Annual (1953-1954),
New York, Medical
Encyclopedia, Inc., 1953, p. 70.

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"They usually produce rest and the sleep brought about by their use approximates normal sleep. The action of these drugs is rapid; and if the patient is not disturbed, the sleep may continue from one to five hours."[1]

Abbott

1. Gurdjian, E. S., and Webster, J. E., Amer. J. of Surgery, 63:236, 1944.

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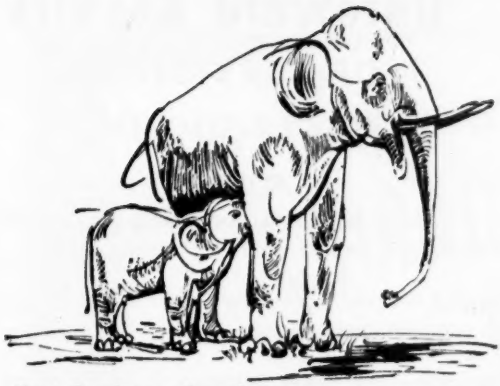

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1. Lampert, L. M.: Milk and Dairy Products, Brooklyn, Chemical Publishing Co., Inc., 1947, p. 10.
2. Gunther, M.: Brit. J. Nutrition 6 (No. 2): 215, 1952.

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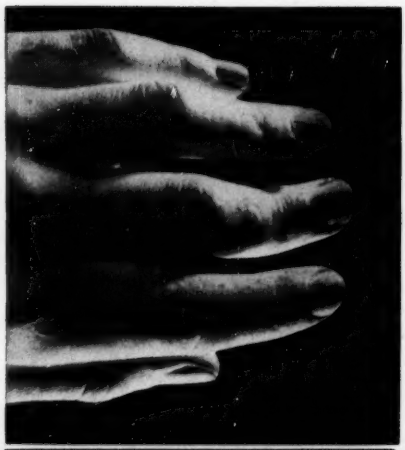

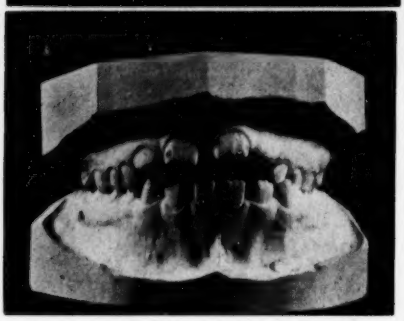

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Hand—sucked two middle fingers left hand since age 4. Note deformity caused.

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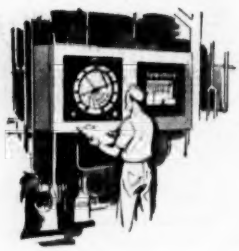

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PROTEIN: The protein of commercial bread is of high biologic value because it is a mixture of wheat flour protein and milk protein, the latter derived from added nonfat milk solids.[4] One pound of enriched bread furnishes about 39 Gm. of protein.

ECONOMY: At its present day low price, bread represents an outstanding nutritional "buy." It provides not only generous amounts of essential nutrients, but also readily available food energy. These features truly make enriched bread one of America's *basic foods.*

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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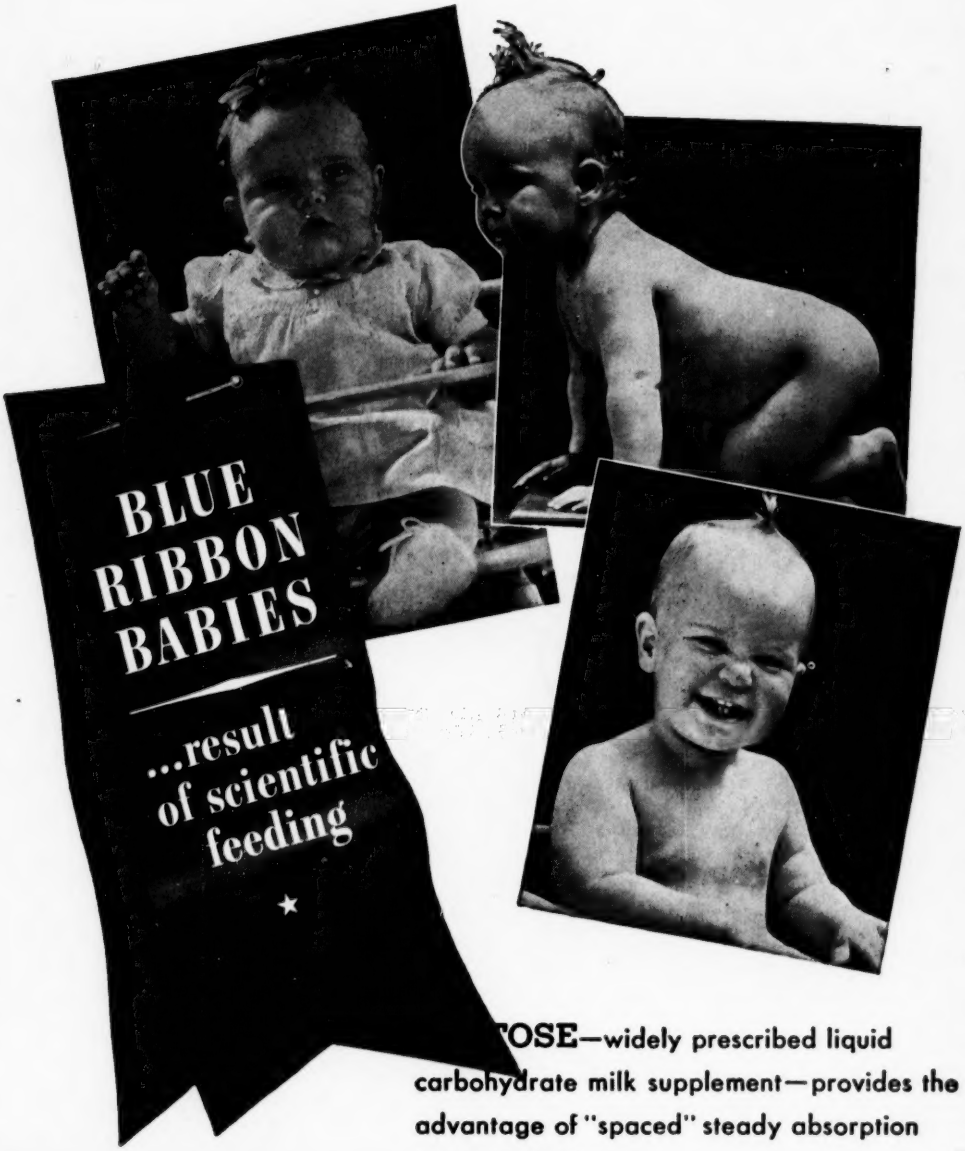

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